

IVERIC
BIO

DEVELOPING TRANSFORMATIVE
THERAPIES
FOR RETINAL DISEASES

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NASDAQ: ISEE

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Safety of Intravitreal Avacincaptad Pegol in Geographic Atrophy: GATHER1 and GATHER2 Results

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Avacincaptad Pegol is an investigational product that has not been evaluated for safety and efficacy by the FDA

Disclosures

Dr. Kaiser

Consultant:

Aerie, Allegro, Allergan, Allgenesis, Alzheon, Annexon Biosciences, AsclepiX, Aviceda, Bayer, Bausch and Lomb, Biogen Idec, Bionic Vision Technologies, Boehringer Ingelheim, Carl Zeiss Meditec, Clearside Biomedical, DeSiTech, DTx Pharma, Duet Therapeutics, Eyevensys, Galecto Biotech, Galimedix, Gemini Therapeutics, Glaukos, Innovent, iRenix, **Iveric Bio**, jCyte, Kanaph Therapeutics, Kanghong, Kodiak, LensGen, NGM Biopharmaceuticals, Inc., Novartis, Ocugenix, Oculis, Ocuphire, OcuTerra Therapeutics Inc., Omeros, Opthea, Oxurion, Palatin, Regeneron, RegenxBio, Retinal Sciences, Retrope, Roivant, Samsung Bioepis, Sandoz, Santen, Stealth Biotherapeutics, Sustained Nano Systems, Takeda, Théa, 2020 Onsite

Avacincaptad pegol: An aptamer which inhibits C5

AVACINCAPTAD PEGOL

- **A pegylated RNA aptamer**
 - Relatively small physical size
 - Synthetic, as opposed to biological, production

Avacincaptad pegol: An aptamer which inhibits C5, leaves the other beneficial parts of the complement system intact

Mol Neurobiol (2016) 53:3076–3087
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Complement Peptide C3a Promotes Astrocyte Survival in Response to Ischemic Stress

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Abstract Astrocytes are the most numerous cells in the central nervous system with a range of homeostatic and regulatory functions. Under normal conditions as well as after ischemia, astrocytes promote neuronal survival. We have previously reported that the complement-derived peptide C3a stimulates neuronal differentiation of neural progenitor cells and protects the immature brain tissue against hypoxic-ischemic injury. Here, we studied the effects of C3a on the response of mouse cortical astrocytes to ischemia. We have found that chemical ischemia, induced by combined inhibition of oxidative phosphorylation and glycolysis, upregulates the expression of C3a receptor in cultured primary astrocytes. C3a treatment protected wild-type but not C3a receptor-deficient astrocytes from cell death induced by chemical ischemia or oxygen-glucose deprivation by reducing ERK signaling and caspase-3 activation. C3a attenuated ischemia-induced upregulation of glial fibrillary acidic protein; however, the protective effects of C3a were not dependent on the presence of the astrocyte intermediate filament system. Pre-treatment of astrocytes with C3a during recovery abrogated the ischemia-induced neuroprotective phenotype of astrocytes. Jointly,

these results provide the first evidence that the complement peptide C3a modulates the response of astrocytes to ischemia and increases their ability to cope with ischemic stress.

Keywords Caspase-3 · Glial fibrillary acidic protein · Ischemia · Neuroprotection

Introduction

Ischemic stroke due to cerebral blood vessel occlusion is the most common form of stroke, characterized by reduced blood flow and supply of oxygen and glucose. Ischemia results in the death of both neurons and glial cells in the ischemic zone. Cells in the ischemic penumbra are metabolically compromised but can be rescued by reconstitution of blood flow or neuroprotective pharmacological intervention. Astrocytes are the most abundant cell type in the mammalian brain. Astrocytes cooperate with neurons at multiple levels, including maintenance of homeostasis, neurotransmitter trafficking and recycling, and defense against oxidative stress [1–5]. Astrocytes also play a role in the maintenance of brain function

C3- and CR3-dependent microglial clearance protects photoreceptors in retinitis pigmentosa

Sean M. Silverman, Wenxin Ma, Xu Wang, Lian Zhao, and Wai T. Wong



Complement activation has been implicated as contributing to neurodegeneration in retinal and brain pathologies, but its role in retinitis pigmentosa (RP), an inherited and largely incurable photoreceptor degenerative disease, is unclear. We found that multiple complement components were markedly up-regulated in retinas with human RP and the rd10 mouse model.

coinciding spatiotemporally with photoactivated retinal microglia. Genetic ablation of complement components reduced retinal inflammatory gene expression. Deficiency of C3 or CR3 disrupted microglial interactions. Deficiency of C3 or CR3 demonstrated neurotoxicity to photoreceptors, demonstrating that C3 and CR3 are required for microglial clearance of apoptotic photoreceptors in RP. These findings provide an interpretation of immunomodulatory therapies in RP.

Complement anaphylatoxin C3a is selectively protective against NMDA-induced neuronal cell death

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The anaphylatoxin C3a is a potent inflammatory polypeptide released at sites of complement activation. To test whether C3a might alter neuronal outcome following an ischemic insult, we determined the effects of purified human C3a on murine primary cortical cell cultures exposed to apoptotic or excitotoxic paradigms. C3a prevented neither serum deprivation-induced apoptotic neuronal death, nor AMPA/kainate-mediated excitotoxicity. However, in mixed cultures of neurons and

astrocytes, C3a dose-dependently protected neurons against NMDA toxicity (47% neuroprotection using 100 nM C3a, $p < 0.01$, $n = 12$). The neuroprotective effect of C3a was observable only in the presence of astrocytes. These observations suggest that C3a is involved in excitotoxicity-mediated neuronal death through astrocyte stimulation and extend its role beyond immune functions. *NeuroReport* 12:289–293 © 2001 Lippincott Williams & Wilkins.

Key words: Anaphylatoxin; Apoptosis; Cerebral ischemia; Complement; Excitotoxicity; N-Methyl-D-aspartate

GATHER 2

Randomized and Treated
(N=447)¹

ACP 2 mg (N=225)		Sham (N=222)	
Discontinued study during Year 1	25	Discontinued study during Year 1	17
Adverse event	3	Adverse event	2
Protocol violation	0	Protocol violation	0
Investigator decision	0	Investigator decision	0
Sponsor decision	0	Sponsor decision	0
Patient request	17	Patient request	13
Loss to follow-up	2	Loss to follow-up	1
Patient noncompliance	1	Patient noncompliance	0
Death	2	Death	1

GATHER 1

Randomized and Treated
(N=286)^{2,3}

ACP 2 mg (N=67)		Sham (N=110)	
Discontinued study	12	Discontinued study	14
Adverse event	0	Adverse event	1
Protocol violation	0	Protocol violation	0
Investigator decision	1	Investigator decision	1
Sponsor decision	5	Sponsor decision	2
Patient request	6	Patient request	8
Loss to follow-up	0	Loss to follow-up	1
Patient noncompliance	0	Patient noncompliance	0
Death	0	Death	1

ACP, avacincaptad pegol.

1. Heier JS, et al. Presented at: AAO; September 30-October 3, 2022; Chicago, IL. 2. Data on file. IVERIC bio; 3. Jaffe GJ, et al. Ophthalmology. 2021;128(4):576-586.

GATHER 2
12 months¹

GATHER 1
12 months^{2,3,a}

	ACP 2 mg (N=225)	Sham (N=222)	ACP 2 mg (N=67)	Sham (N=110)
TEAEs, n (%)	178 (79.1)	157 (70.7)	50 (74.6)	77 (70.0)
Ocular in study eye	110 (48.9)	83 (37.4)	35 (52.2)	38 (34.5)
Non-ocular	125 (55.6)	127 (57.2)	39 (58.2)	60 (54.5)
Serious TEAEs, n (%)	30 (13.3)	37 (16.7)	7 (10.4)	20 (18.2)
Ocular in study eye	2 (0.9)	2 (0.9)	0	0
Non-ocular	29 (12.9)	35 (15.8)	7 (10.4)	20 (18.2)
TEAEs leading to study drug discontinuation, n (%)	6 (2.7)	2 (0.9)	0	1 (0.9)
Ocular in study eye	2 (0.9)	0	0	0
Non-ocular	4 (1.8)	2 (0.9)	0	1 (0.9)

^aBoth ACP and sham groups are a combination of Part 1 and Part 2.

Note: N = study eyes with events. A patient with multiple occurrences of an AE under one treatment is counted only once.

ACP, avacincaptad pegol.

1. Heier JS, et al. Presented at: AAO; September 30-October 3, 2022; Chicago, IL; 2. Data on file. IVERIC bio; 3. Jaffe GJ, et al. Ophthalmology. 2021;128(4):576-586.

GATHER 2

12 months¹

GATHER 1

12 months^{2,3,a}

Ocular TEAEs, n (%)	12 months ¹		12 months ^{2,3,a}	
	ACP 2 mg (N=225)	Sham (N=222)	ACP 2 mg (N=67)	Sham (N=110)
Conjunctival hemorrhage	27 (12.0)	17 (7.7)	10 (14.9)	13 (11.8)
Punctate keratitis	11 (4.9)	14 (6.3)	4 (6.0)	8 (7.3)
Conjunctival hyperemia	12 (5.3)	13 (5.9)	3 (4.5)	4 (3.6)
Choroidal neovascularization	15 (6.7)	9 (4.1)	6 (9.0)	3 (2.7)
Dry eye	8 (3.6)	8 (3.6)	0	2 (1.8)
Eye pain	9 (4.0)	6 (2.7)	2 (3.0)	3 (2.7)
Vitreous detachment	7 (3.1)	6 (2.7)	2 (3.0)	5 (4.5)
Visual acuity reduced	3 (1.3)	5 (2.3)	2 (3.0)	4 (3.6)
Vision blurred	6 (2.7)	2 (0.9)	1 (1.5)	2 (1.8)
Visual impairment	6 (2.7)	2 (0.9)	0	0
Intraocular pressure increased	21 (9.3)	2 (0.9)	4 (6.0)	1 (0.9)
Vitreous floaters	6 (2.7)	1 (0.5)	1 (1.5)	1 (0.9)
Visual acuity reduced transiently	6 (2.7)	1 (0.5)	---	---
Blepharitis	6 (2.7)	0	0	1 (0.9)
Ocular hypertension	5 (2.2)	0	---	---

^aBoth ACP and sham groups are a combination of Part 1 and Part 2.

Note: N = study eyes with events. A patient with multiple occurrences of an AE under one treatment is counted only once; --- indicates data not collected.

ACP, avacincaptad pegol; TEAE, treatment emergent adverse event.

1. Heier JS, et al. Presented at: AAO; September 30-October 3, 2022; Chicago, IL; 2. Data on file. IVERIC bio. 3. Jaffe GJ, et al. Ophthalmology. 2021;128(4):576-586.

GATHER 2
12 months¹

GATHER 1
12 months^{2,a}

	ACP 2 mg (N=225)	Sham (N=222)	ACP 2 mg (N=67)	Sham (N=110)
Ocular serious TEAEs in study eye, n (%)	2 (0.9)	2 (0.9)	0	0
Choroidal neovascularization	2 (0.9)	1 (0.5)	0	0
Visual acuity reduced	0	1 (0.5) ^b	0	0
Visual acuity reduced transiently	0	1 (0.5) ^b	0	0

^aBoth ACP and sham groups are a combination of Part 1 and Part 2.

^bOccurred in the same patient.

Note: N = study eyes with events. A patient with multiple occurrences of an AE under one treatment is counted only once.

ACP, avacincaptad pegol; TEAE, treatment emergent adverse event.

1. Heier JS, et al. Presented at: AAO; September 30-October 3, 2022; Chicago, IL; 2. Data on file. IVERIC bio.

GATHER 2
12 months¹

GATHER 1
12 months^{2,3,a,b}

	ACP 2 mg (N=225)	Sham (N=222)	ACP 2 mg (N=67)	Sham (N=110)
Intraocular inflammation, n	0	0	1 (1.5)	0
Endophthalmitis, n	0	0	0	0
Ischemic optic neuropathy, n	0	0	0	0

^aBoth ACP and sham groups are a combination of Part 1 and Part 2.

^bThere was 1 case of ischemic optic neuropathy in the ACP 2 mg group in GATHER1 at 18 months.

ACP, avacincaptad pegol.

1. Heier JS, et al. Presented at: AAO; September 30-October 3, 2022; Chicago, IL; 2. Data on file. IVERIC bio; 3. Jaffe GJ, et al. Ophthalmology. 2021;128(4):576-586.

	GATHER 2 12 months ¹		GATHER 1 12 months ^{2,a}	
	ACP 2 mg (N=225)	Sham (N=222)	ACP 2 mg (N=67)	Sham (N=110)
Total CNV, n (%)	15 (6.7)	9 (4.1)	6 (9.0)	3 (2.7)

- In GATHER1, if CNV developed in the study eye during the study, the patient was withdrawn from the study
- In GATHER2, suspected development of CNV in the study eye by the principal investigator triggered full imaging workup assessed with FP, FA, and OCT and confirmed by the Duke Reading Center within 1 hour of submission
 - If the diagnosis was confirmed, the patient continued receiving the study treatment in the trial, and the study eye was also treated with ranibizumab or aflibercept according to the country label
 - No patients in GATHER2 received anti-VEGF therapy without a Duke-confirmed CNV diagnosis
 - All Month 12 imaging (FA, FP and OCT) was evaluated by the Duke Reading Center for CNV, irrespective of suspicion by the principal investigator

^aBoth ACP and sham groups are a combination of Part 1 and Part 2.

ACP, avacincaptad pegol; CNV, choroidal neovascularization; FA, fluorescein angiography; FP, fundus photography; OCT, optical coherence tomography.

1. Heier JS, et al. Presented at: AAO; September 30-October 3, 2022; Chicago, IL; 2. Jaffe GJ, et al. Ophthalmology. 2021;128(4):576-586.

	GATHER 2 12 months ¹		GATHER 1 12 months ^{2,3,a}	
	ACP 2 mg (N=225)	Sham (N=222)	ACP 2 mg (N=67)	Sham (N=110)
Total CNV, n (%)	15 (6.7)	9 (4.1)	6 (9.0)	3 (2.7)
eMNV, n (%)	11 (4.9)	7 (3.2)	4 (6.0)	3 (2.7)
neMNV, n (%)	1 (0.4)	0	2 (3.0)	0
Peripapillary NV, n (%)	3 (1.3)	2 (0.9)	0	0

- Exudation status was read by the CORE Reading Center at Cole Eye Institute of the Cleveland Clinic
- OCT images were read to determine the number of CNV cases that were (1) macular neovascularization (MNV), versus peripapillary neovascularization and (2) exudative vs. non-exudative

The Reading Center classifies cases of MNV as exudative or non-exudative based on the following OCT criteria:

- **"eMNV"** is MNV that presents with new onset fluid in either the subretinal space or the intraretinal space
- **"neMNV"** is MNV which does not present with new onset fluid in the subretinal or intraretinal spaces. In some cases, isolated fluid may be present in the sub-RPE space. A case is considered to be neMNV when the MNV may not be visible but both a double-layer sign and sub-RPE fluid are present

^aBoth ACP and sham groups are a combination of Part 1 and Part 2. ACP, avacincaptad pegol; CNV, choroidal neovascularization; CORE, Center for Ocular Research and Evaluation; eMNV, exudative MNV; neMNV, non-exudative MNV; NV, neovascularization; OCT, optical coherence tomography; RPE, retinal pigment epithelium.

1. Heier JS, et al. Presented at: AAO; September 30-October 3, 2022; Chicago, IL; 2. Data on file. IVERIC bio. 3. Jaffe GJ, et al. Ophthalmology. 2021;128(4):576-586.

In GATHER2, there were no cases of intraocular inflammation, endophthalmitis and ischemic optic neuropathy in study eyes treated with avacincaptad pegol 2 mg at Month 12

- Results were consistent with GATHER1 at 12 months, except for 1 case of intraocular inflammation

- In GATHER 2, CNV rates were 6.7% in the avacincaptad pegol 2 mg group and 4.1% in the sham group
- In GATHER 1, CNV rates were 9.0% in the avacincaptad pegol 2 mg group and 2.7% in the sham group

Avacincaptad pegol is the first investigational therapy in GA to achieve the 12-month, prespecified, primary objective vs. sham, coupled with a consistent safety profile, in two pivotal, phase 3 studies

Thank you to the GATHER program
investigators, research staff, and patients

