Published in final edited form as:
Ophthalmology. 2014 August ; 121(8): 1663–1664.e1. doi:10.1016/j.ophtha.2014.02.025.

Endothelial PAS domain-containing protein 1 (*EPAS1*) Gene Polymorphisms and Response to Anti-VEGF Therapy in the Comparison of AMD Treatments Trials (CATT)

Stephanie A Hagstrom, PhD[1,2], **Gui-shuang Ying, PhD**[3], **Gayle JT Pauer, BA**[1], **Jiayan Huang, MS**[3], **Maureen G Maguire, PhD**[3], and **Daniel F Martin, MD**[1,2] **for the CATT Research Group**

[1]Cole Eye Institute, Cleveland Clinic, Cleveland, OH

[2]Department of Ophthalmology, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

[3]Department of Ophthalmology, University of Pennsylvania, Philadelphia, PA

The efficacy of the intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents bevacizumab and ranibizumab has revolutionized the treatment of neovascular age-related macular degeneration (nAMD). Results from the Comparison of AMD Treatments Trials (CATT), the Alternative Treatments to Inhibit VEGF in Patients with Age-Related Choroidal Neovascularisation (IVAN) trial, and other multicenter randomized clinical trials that compared bevacizumab and ranibizumab indicate that both drugs provide dramatic and lasting visual improvements in patients. However, results from these trials also make clear that there is individual variation in the initial response to therapy and in the durability of the clinical effect. Genetic assessment of participants in these trials provides an ideal opportunity to investigate pharmacogenetic associations using rigorously defined phenotypic data.

A recent report from the IVAN Study Group evaluated 509 participants across 494 SNPs for evidence of a genetic association with response to anti-VEGF therapy as measured by change in total retinal thickness (TRT) in one year.[1] Eyes in the highest quartile of change in TRT (n=126) were designated as responders while those in the lowest quartile (n=128) were designated as non-responders. The strongest association observed was for rs9679290 in the *EPAS1* gene (unadjusted p = 0.002); however, the association was not statistically significant after Bonferroni correction for multiple comparisons (p = 0.84). Interestingly,

Corresponding Author: Stephanie A Hagstrom, PhD, Ophthalmic Research - i31, Cole Eye Institute, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, hagstrs@ccf.org, Phone: 216-445-4133, Fax: 216-445-3670.

Conflict of Interest: No conflicting relationship exists for any author.

four of the top ten strongest associations from the IVAN study were in this gene, although none of them were statistically significant after Bonferroni correction.

EPAS1 represents a plausible candidate gene for influencing anti-VEGF treatment response. It is a transcription factor expressed predominantly in highly vascularized tissues and likely regulates vascularization.[2] *Epas1*−/− mice demonstrate severe retinopathy at a young age, including photoreceptor loss, retinal thinning, and abnormal retinal vasculature.[3]

In an effort to replicate the pharmacogenetic association between *EPAS1* SNPs and response to anti-VEGF therapy, we evaluated the top four *EPAS1* SNPs from the IVAN study (rs6726454, rs7589621, rs9679290, and rs12712973) in 831 CATT participants.[4] Similar to IVAN, we classified participants as responders or non-responders to anti-VEGF therapy based on TRT as determined by optical coherence tomography (OCT). We calculated the change in TRT from baseline at the latest time point for which OCT data were available through one year (4, 8, 12, 24, or 52 weeks). Eyes with changes in TRT greater than or equal to the 75th percentile or more were classified as responders, and those with changes less than or equal to the 25th percentile or lower were classified as non-responders.

Two hundred eleven participants were classified as responders and 210 were classified as non-responders. The distribution of change in total retinal thickness in CATT was remarkably similar to that seen in IVAN (Figure 1, available at www.aaojournal.org). The genotypic frequencies of all four SNPs in CATT were also similar to that seen in IVAN (Table 1). In the CATT patient cohort, no statistically significant association was observed for any of the genotypes at the four *EPAS1* SNPs. Similar to the IVAN result, the strongest association was at rs9679290 (p=0.21); however, the odds ratio was in the opposite direction (0.84 for CATT, 1.87 for IVAN). The other three *EPAS1* SNPs (rs6726454, rs12712973, rs7589621) were also not associated with response to therapy in CATT, also with odds ratios in the opposite direction as seen in IVAN.

The CATT data does not support a pharmacogenetic association between the four SNPs tested in *EPAS1* and response to anti-VEGF therapy in patients with nAMD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial Support: Supported by cooperative agreements U10 EY017823, U10 EY017825, U10 EY017826, and U10 EY017828 from the National Eye Institute, National Institutes of Health, Department of Health and Human Services.

The sponsor or funding organization had no role in the design or conduct of this research.

References

1. Lotery AJ, Gibson J, Cree AJ, et al. Pharmacogenetic Associations with Vascular Endothelial Growth Factor Inhibition in Participants with Neovascular Age-Related Macular Degeneration in the IVAN Study. Ophthalmol. 2013; 120:2637–43.

2. Tian H, McKnight SL, Russell DW. Endothelial PAS domain protein 1 (EPAS1), a transcription factor selectively expressed in endothelial cells. Genes Dev. 1997; 11:72–82. [PubMed: 9000051]

3. Ding K, Scortegagna M, Seaman R, et al. Retinal disease in mice lacking hypoxia-inducible transcription factor-2alpha. Invest Ophthalmol Vis Sci. 2005; 46:1010–6. [PubMed: 15728559]

4. Hagstrom SA, Ying G-S, Pauer GJT, et al. Pharmacogenetics for genes associated with age-related macular degeneration in the Comparison of AMD Treatments Trials (CATT). Ophthalmol. 2013; 120:593–9.

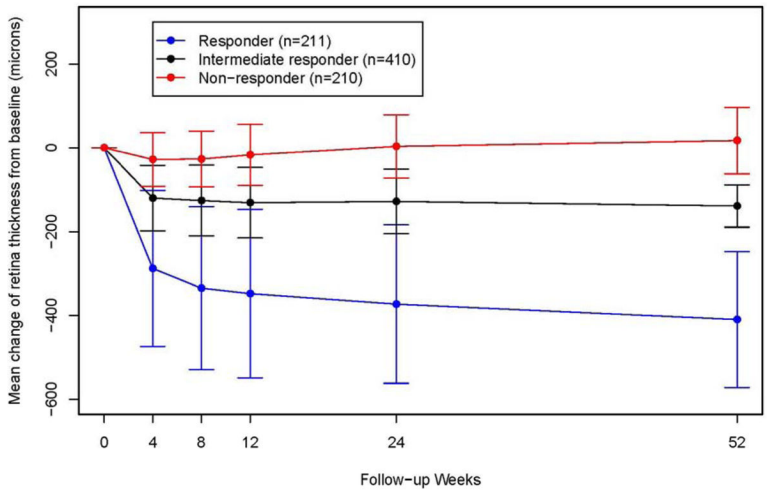

Figure 1.

Mean (+/−Standard Deviation) change of total retinal thickness (microns) from baseline in the Comparison of AMD Treatments Trials (CATT).

Table 1

Association of *EPAS1* genotype and morphologic response in CATT (N=421)

	Good response group (%)	Poor response group (%)	Odds Ratio (95% CI)	Linear Trend P value
rs9679290				
CC	40 (19.0)	51 (24.3)		
CG	108 (51.2)	103 (49.0)		
GG	63 (29.9)	56 (26.7)		
CAD Frequency (%) of Allele C	188 (44.6)	205 (48.8)	0.84 (0.64,1.11)	0.21
IVAN Frequency (%) of Allele C	(52)	(36)	1.87	
rs6726454				
GG	49 (23.2)	56 (26.7)		
AG	102 (48.3)	105 (50.0)		
AA	60 (28.4)	49 (23.3)		
CAD Frequency (%) of Allele G	200 (47.4)	217 (51.7)	0.84 (0.65,1.11)	0.22
IVAN Frequency (%) of Allele G	(56)	(42)	1.80	
rs12712973				
AA	51 (24.2)	43 (20.5)		
AC	108 (51.2)	109 (51.9)		
CC	52 (24.6)	58 (27.6)		
CAD Frequency (%) of Allele A	210 (49.8)	195 (46.4)	1.15 (0.87,1.51)	0.33
IVAN Frequency (%) of Allele A	(41)	(54)	0.59	
rs7589621				
AA	12 (5.7)	14(6.7)		
AG	85 (40.3)	92 (43.8)		
GG	114 (54.0)	104 (49.5)		
CAD Frequency (%) of Allele A	109 (25.8)	120 (28.6)	0.86 (0.63,1.18)	0.36
IVAN Frequency (%) of Allele A	(29)	(20)	1.70	

CAD: Comparison of AMD Treatments Trials

IVAN: Alternative Treatments to Inhibit VEGF in Patients with Age-Related Choroidal Neovascularisation

CI: confidence interval