Abstract


CFH and ARMS2 Genetic Polymorphisms Predict Response to Antioxidants and Zinc in Patients with Age-related Macular Degeneration.

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OBJECTIVE: The Age-Related Eye Disease Study (AREDS) demonstrated that antioxidant and zinc supplementation decreases progression to advanced age-related macular degeneration (AMD) in patients with moderate to severe disease. We evaluated the interaction of genetics and type of nutritional supplement on progression from moderate to advanced AMD.

DESIGN: Genetic analysis of a randomized, prospective clinical trial.

PARTICIPANTS: White patients with AREDS category 3 AMD in 1 eye and AREDS categories 1 through 4 AMD in the fellow eye enrolled in the AREDS with available peripheral blood-derived DNA (995).

METHODS: Subjects were evaluated for known AMD genetic risk markers and treatment category. The progression rate to advanced AMD was analyzed by genotypes and AREDS treatment group using Cox regression.

MAIN OUTCOME MEASURES: The effect of inherited gene polymorphisms on treatment group-specific rate of progression to advanced AMD.

RESULTS: Over an average of 10.1 years, individuals with 1 or 2 complement factor H (CFH) risk alleles derived maximum benefit from antioxidants alone. In these patients, the addition of zinc negated the benefits of antioxidants. Treatment with zinc and antioxidants was associated with a risk ratio (RR) of 1.83 with 2 CFH risk alleles (P = 1.03E-02), compared with outcomes for patients without CFH risk alleles. Patients with age-related maculopathy sensitivity 2 (ARMS2) risk alleles derived maximum benefit from zinc-containing regimens, with a deleterious response to antioxidants in the presence of ARMS2 risk alleles. Treatment with antioxidants was associated with an RR of 2.58 for those with 1 ARMS2 risk allele and 3.96 for those with 2 ARMS2 risk alleles (P = 1.04E-6), compared with patients with no ARMS2 risk alleles. Individuals homozygous for CFH and ARMS2 risk alleles derived no benefit from any category of AREDS treatment.

CONCLUSIONS: Individuals with moderate AMD could benefit from pharmacogenomic selection of nutritional supplements. In this analysis, patients with no CFH risk alleles and with 1 or 2 ARMS2 risk alleles derived maximum benefit from zinc-only supplementation. Patients with one or two CFH risk alleles and no ARMS2 risk alleles derived maximum benefit from antioxidant-only supplementation; treatment with zinc was associated with increased progression to advanced AMD. These recommendations could lead to improved outcomes through genotype-directed therapy.

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