Pharmacogenomics for the Retina Specialist

This specialized discipline may play an important role in improving patient outcomes.

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Pharmacogenomics, an evolving research discipline within ophthalmology, investigates genotype-phenotype correlations in an attempt to explain interpatient variability in response to medications. To date, most ophthalmologic pharmacogenomics research has concerned the treatment of open-angle glaucoma and age-related macular degeneration (AMD).

OPEN-ANGLE GLAUCOMA

Both primary open-angle glaucoma (POAG) and steroid-induced ocular hypertension have been studied using pharmacogenomic approaches. Pharmacologic strategies to reduce intraocular pressure (IOP) remain the leading treatments for POAG and allied disorders. However, an unpredictable rate of nonresponse to medication is a long-standing clinical challenge. For example, in one randomized clinical trial, the rate of nonresponse (defined as reduction of IOP by less than 15% from baseline) was reported as 28% with timolol and 18% with latanoprost.[1] The precise mechanisms for this variability remain largely undetermined. Pharmacogenomics has been suggested as an approach to investigate this clinically important phenomenon.[2,3]

The topical β-blockers comprise multiple nonselective agents (β_1- and β_2-antagonists), including timolol, and one β_1-selective agent, betaxolol. The β_1-adrenergic receptor gene, *ADRB1*, contains two single nucleotide polymorphisms.[4] The β_2-adrenergic receptor gene, *ADRB2*, contains four polymorphisms.[5] In a prospective, nonrandomized clinical trial, 48 normal volunteers were treated with betaxolol for 6 weeks. The Arg389 homozygote genotype independently correlated with higher baseline IOP and a greater magnitude of response to betaxolol, even after adjusting for baseline IOP.[6]

In a prospective clinical trial, 89 normal volunteers were treated with timolol. No statistically significant association was found between the clinical effectiveness of timolol and three polymorphisms in the β_2-adrenergic receptor gene.[7]

The etiology of the steroid response has never been fully explained, but a genetic determinant has long been suspected.

Latanoprost is a highly selective agonist against the prostaglandin $F_{2\alpha}$ (FP) receptor.[8] In a prospective, nonrandomized clinical trial, 100 normal volunteers were treated with latanoprost for 1 week. The polymorphisms rs3753380 and rs3766355 showed statistically significant associations with the clinical efficacy of latanoprost.[9]

More recently, the phenomenon of steroid-induced glaucoma has been studied with pharmacogenomic approaches. The etiology of the steroid response has never been fully explained, but a genetic determinant has long been suspected.[10] Intravitreal triamcinolone acetonide (IVTA) is used to treat a variety of retinal diseases, including exudative age-related macular degeneration[11] and macular edema secondary to diabetes mellitus,[12] retinal vein occlusion,[13] and other causes. Clinically significant elevation of IOP has been reported in about 40% of patients.[14]

The gene *MYOC* is expressed in the trabecular meshwork, and its expression has been shown to be steroid-induced. Variations in *MYOC* may occur in about 5% of patients with open-angle glaucoma. However, there is no statistically significant association between *MYOC* mutations and steroid-induced glaucoma.[15] In cadaver eyes, timolol reduced *MYOC* expression in some cases, but timolol does not affect *MYOC* induction by dexamethasone.[16]

Glucocorticoid receptors are present in the trabecular meshwork, suggesting a possible etiology of steroid-induced glaucoma.[17] In a pilot study, 52 patients were treated with IVTA for a variety of retinal diseases. There

were no statistically significant associations between six common polymorphisms in the glucocorticoid receptor gene and the magnitude of IOP elevation following treatment with IVTA.[18]

AGE-RELATED MACULAR DEGENERATION

The primary treatment for nonexudative AMD is vitamin supplementation to prevent progression to advanced disease.[19] For patients with exudative AMD, the MARINA and ANCHOR trials demonstrated, respectively, the efficacy of ranibizumab in the treatment of minimally classic or occult choroidal neovascularization[20] and the superiority of ranibizumab to photodynamic therapy with verteporfin in patients with predominantly classic CNV.[21] Bevacizumab is also widely used to treat exudative AMD.[22]

A polymorphism in the complement factor H gene (*CFH*) has been associated with an increased risk of AMD.[23-26] In a retrospective analysis of a subgroup of patients from the Age-Related Eye Disease Study (AREDS), 876 patients with AREDS categories 3 and 4 were genotyped for polymorphisms in *CFH*. In patients with the *CFH* TT genotype, treatment with antioxidants plus zinc was associated with a 68% risk reduction. In patients with the *CFH* CC genotype, treatment with antioxidants plus zinc was associated with only an 11% risk reduction. These differences in risk reduction were statistically significant.[27]

In a retrospective cohort study of 86 patients with exudative AMD treated with bevacizumab, patients with the *CFH* TC and TT genotypes experienced more favorable visual outcomes than did patients with the *CFH* CC genotype, even after adjusting for age, pretreatment visual acuity, and CNV lesion size.[28]

In a retrospective study of 156 patients with exudative AMD treated with ranibizumab, there were no differences in visual outcomes related to the *CFH* genotype, but a statistically significant genetic "dose-response" effect was noted with regard to the number of injections required. Over a 9-month period, patients with the *CFH* TT genotype required a mean of 3.3 injections, patients with the *CFH* TC genotype required a mean of 3.8 injections, and patients with the *CFH* CC genotype required a mean of 3.9 injections.[29]

In a retrospective study of 69 patients with exudative AMD treated with verteporfin, patients with the *CFH* TT genotype experienced poorer visual outcomes than did patients with the *CFH* TC or CC genotypes, even after adjusting for age, pretreatment visual acuity, and CNV lesion type.[30] These results appear to contrast with the results from a previous series of 27 patients treated with verteporfin, in which the *CFH* CC genotype was associated with a greater degree of posttreatment visual loss than the TC genotype. However, in this series, the number of patients with the TT genotype (2) was too small for statistical analysis.[31]

IMPLICATIONS FOR THE PRACTICING RETINAL SPECIALIST

Interpatient variability in response to medications remains an important daily clinical challenge in all specialties of medicine. For example, although the majority of patients with elevated IOP will respond to topical β-blockers or prostaglandin analogues, there is no reliable way to identify the nonresponders in advance. Similarly, although only a minority of patients treated with IVTA will develop a steroid response, again there is no reliable way to identify these patients prior to treatment. Therefore, all treated patients must be followed to determine the response, which at the very least leads to additional clinic visits and exposure to additional medications in at least some patients. Pharmacogenomics may provide some assistance with this problem. For example, knowledge of an individual patient's risk of developing a steroid response might influence the decision to treat a patient with IVTA or one of the longer-acting corticosteroid preparations.

Based on currently available data, there appears to be a complex relationship between *CFH* variants and response to interventions to treat AMD. The *CFH* CC polymorphism appears to be associated with relatively poorer outcomes following treatment with antioxidants plus zinc to prevent progression, and with relatively poorer outcomes following treatment with bevacizumab for CNV. However, this polymorphism may be associated with relatively better visual outcomes following treatment with verteporfin. Additional studies are necessary to validate all of these initial findings, but pharmacogenomics appears to hold great promise to improve patient care. ■

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