INTEGRATIVE MEDICINE SECTION

Brief Research Report

Genetic Predictors of Response to Acupuncture for Aromatase Inhibitor–Associated Arthralgia Among Breast Cancer Survivors

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Abstract

Objective. To evaluate the associations between polymorphisms in two genes, catechol-O-methyltransferase and T-cell leukemia/lymphoma 1A, and acupuncture-mediated pain reduction among breast cancer survivors with aromatase inhibitor–associated arthralgia.

Design, Setting, and Subjects. Biospecimens were obtained from 38 patients enrolled in a clinical trial of acupuncture for aromatase inhibitor–associated arthralgia in postmenopausal hormone receptor–positive breast cancer survivors.

Methods. We used polymerase chain reaction to genotype the rs4680 (Val158Met) and rs4633 (His62His) variants in the catechol-O-methyltransferase gene and rs2369049 (A>G) and rs7158782 (A>G) variants in the T-cell leukemia/lymphoma 1A gene. Response to acupuncture was defined by 30% reduction in end-of-treatment average pain, measured by the Brief Pain Inventory. We used Fisher exact tests to evaluate associations between genotype and treatment response.

Results. Among participants, all six (15.8%) subjects who expressed AA in locus rs4680 responded to acupuncture. In a combined analysis, the 18 (47.4%) subjects with the responder genotype at either rs4680 (AA) or rs2369049 (GG or AG) were significantly more likely to respond to acupuncture than those without (77.8% vs 45.0%, $P = 0.039$).

Conclusions. Specific genetic variations at loci rs4680 and rs2369049 are associated with response to acupuncture-type intervention for management of arthralgia. These results serve as a proof of concept for applying a precision medicine framework to the study of cancer pain management.

Key Words. Acupuncture; Alternative Medicine; Joint; Musculoskeletal; Pain Management; Treatment Outcome

Introduction

Arthralgia, or joint pain, is a common and debilitating symptom that affects almost half of breast cancer survivors who use aromatase inhibitors (AIs) [1], medications that inhibit estrogen production. Aromatase inhibitor–associated arthralgia (AIAA) is associated with functional impairment [2] and premature discontinuation of potentially life-saving treatment [3]. Precision medicine is a framework that utilizes information concerning patient genotype and biomarkers to guide treatment and better quantify prognosis [4]. Studies in precision medicine have produced advancements in cancer treatment, yet

precision medicine has not yet been used to study management of pain in cancer survivors.

Acupuncture is a nonpharmacological treatment modality that is rapidly gaining popularity among cancer patients and survivors for the management of cancer symptoms including pain [5,6]. Emerging evidence suggests that acupuncture may be effective in treating AIAA [7]; however, it is unknown which specific patients may benefit. We sought to explore associations between treatment response to acupuncture and single nucleotide polymorphisms (SNPs) in the Catechol-O-Methyltransferase (COMT) and T-Cell Leukemia/Lymphoma 1A (TCL1A) genes in patient samples from a completed clinical trial [8]. Due to a limited sample size, we chose to focus on SNPs associated with the COMT gene including rs4680, a well-characterized polymorphism associated with the COMT gene. The G allele is more common than the A allele, which confers a Val158Met substitution in the catechol-O-methyltransferase enzyme that results in a threefold reduction in enzyme activity [9]. In both oncologic and nononcologic clinical settings, individuals carrying one or two copies of the Met (A) allele have a unique clinical phenotype characterized by higher self-reported levels of pain [10–12] that requires lower opioid dosages for pain relief [13–15]. We chose to focus on SNPs associated with the TCL1A gene because a prior genome-wide association study identified associations between SNPs including rs2369049 and the presence of AIAA [16]. We hypothesize that patient genotype at single nucleotide polymorphisms may predict superior response to acupuncture for AIAA in breast cancer survivors.

Methods

The data used in this analysis were obtained from biospecimens and patient-reported outcomes from participants in a randomized controlled trial that evaluated the preliminary efficacy of electro-acupuncture and sham acupuncture for treatment of AIAA (Clinical Trial Registration NCT01013337). The institutional review board of the University of Pennsylvania approved the original trial, which allowed for biospecimen storage and exploratory analyses. The details of the trial and primary findings have been previously reported [8]. In brief, participants were postmenopausal survivors of stage I–III hormone receptor–positive breast cancer who were currently using an AI (Anastrozole, Letrozole, or Exemestane), had joint pain that they attributed to their AI for at least three months, reported a worst pain rating of at least 4 or greater on an 11-point (0–10) numerical rating scale in the preceding week, reported at least 15 days with pain in the preceding 30 days, and signed the informed consent. We excluded individuals who had metastatic (stage IV) breast cancer or who had a history of a bleeding disorder.

Of the 67 total participants, 44 were randomized to acupuncture intervention, and 23 were assigned to waitlist control. Of the 44 participants receiving active

intervention, 38 provided complete data, including biospecimens and self-reported outcomes that are included in the present analysis. Participants in the acupuncture intervention groups received 10 treatments over eight weeks. Acupuncture was delivered based on a manualized protocol that involved needling at least four local points around the joint with the most pain in addition to at least four distant points to address constitutional symptoms such as depression/anxiety and fatigue that are commonly seen in conjunction with pain; needles were left in place for 30 minutes. All participants were educated on joint pain, physical activity, and continuing with current medical treatments (including prescription and over-the-counter pain medications) as usual.

Genomic DNA was extracted from stored blood samples using the Qiagen QiaAmp 96 DNA Blood Kit (Valencia, CA, USA). Laboratory personnel were blinded to all clinical and outcome data. Genotypes were obtained by oligonucleotide ligation/polymerase chain reaction and capillary electrophoresis for the rs4680 (Val158Met) and rs4633 (His62His) variants in COMT and the rs2369049 (A > G) and rs7158782 (A > G) variants in TCL1A using the Applied Biosystems' SNPLex platform (Foster City, CA, USA).

The primary outcome of interest was pain intensity measured by the Brief Pain Inventory, which has previously demonstrated reliability, validity, and sensitivity to change in assessment of pain in cancer patients [17]. Participants were responders to acupuncture if they achieved a clinically significant 30% reduction in end-of-treatment average pain intensity score [18].

Data analysis was performed using STATA 10.0 for Windows (STATA Corporation, College Station, TX, USA). The sample size was determined by the parent trial. Association between genotype and treatment response for the 38 participants was evaluated by comparing the proportion of responders among each genotype. Fisher exact tests were conducted to evaluate linkage disequilibrium and the association between specific single or combined SNPs and treatment response.

Results

Among 38 trial participants, 60.5% met criteria for treatment response. The SNP most strongly associated with response to acupuncture was rs4680. Six (15.8%) subjects expressed AA, and all responded to acupuncture, which was nonsignificantly greater than those with at least one G allele (53.1% response rate, $P=0.063$). Sixteen (42.1%) subjects had AA/AG on rs2369049 and were nonsignificantly more likely to respond to acupuncture than those with GG (75% vs 50%, $P=0.18$) (Table 1).

We identified linkage disequilibrium between rs4680 and rs4633 ($P<0.001$) and between rs2369049 and rs7158782 ($P<0.001$). Subjects were categorized as having the responder genotype if they expressed either

Table 1 Single-SNP analyses of acupuncture response by genotype

	COMT				TCL1A			
	rs4680		rs4633		rs2369049		rs7158782	
	AA	AG or GG	CC or CT	TT	GG	GA or AA	AA	AG or GG
Proportion, %	15.8	84.2	86.8	13.2	57.9	42.1	52.6	47.4
Responder, %	100	53.1	54.6	100	50	75	50	72.2
<i>P</i> value		0.063		0.136		0.18		0.198

the AA genotype at rs4680 or the AA or AG genotype at rs2369049; 20 participants (52.6%) had this combination. We observed a significant effect of genotype on acupuncture response ($P=0.039$), with a 77.8% (14/18) response rate among subjects with the responder genotype compared with a rate of 45% (9/20) among subjects with the nonresponder genotype (Table 2).

Discussion

The application of a precision medicine framework in pain management for cancer survivors represents an important scientific and clinical opportunity. In this exploratory study, we found that the presence of either both A alleles at rs4680 (COMT) or at least one A allele at rs2369049 (TCL1A) was associated with a higher likelihood of pain reduction in response to acupuncture-type intervention for AIAA.

The results are consistent with prior evidence that the A allele at rs4680 causes higher prefrontal cortex dopamine concentrations [9] and is associated with greater response to pain management intervention [13–15]. On functional magnetic resonance imaging, individuals carrying the Met (A) allele demonstrated decreased neural connectivity to the frontal gyrus in response to acupuncture, which was not observed in individuals homozygous for the Val (G) allele [19]. We propose that the genotype at the rs4680 locus mediates response to acupuncture intervention by a mechanism involving variation in levels of catecholamine neurotransmission in the frontal cortex.

Similarly, the results are consistent with the literature implicating the A allele at rs2369049 in greater expression of nuclear factor κ B (NF- κ B) in response to estrogen deprivation [16,20,21]. In the current study, individuals with at least one A allele were more likely to respond positively to acupuncture. On the basis of prior findings in animals that NF- κ B is downregulated by acupuncture [22,23], we suggest that the preferential response of individuals with the A allele occurs via a mechanism involving NF- κ B.

Our study has a number of limitations. Due to a small sample size of 38 participants, the study could not be stratified by race or acupuncture type and was powered

Table 2 Combined SNP analysis

	Genotype	
	Responder*	Nonresponder†
Acupuncture responder	14	8
Acupuncture nonresponder	4	10
<i>P</i> value	0.039	

*Responder genotype is AA at rs4680 or AA/AG at rs2369049.

†Nonresponder genotype is both AG/GG at rs4680 and GG at rs2369049.

to reach statistical significance only in the combined analysis. The analyses were post hoc in nature after the trial was completed. The promising preliminary findings warrant additional validation in a larger study, and further investigation of the relationship between genotype and response to pain management could yield information useful for guiding personalized pain management for women with breast cancer.

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