The Intensive Diet and Exercise for Arthritis Trial: 18-Month Clinical Outcomes

Written by Debra Gordon, MS

Excess weight is a well-established risk factor for osteoarthritis (OA). The Arthritis, Diet, and Activity Promotion Trial (ADAPT) demonstrated for the first time that exercise that is combined with calorie restriction, designed to reduce body mass index (BMI), could also improve physical function and reduce knee pain [Messier SP et al. *Arthritis Rheum* 2004]. The trial, however, did not demonstrate any effect of diet and exercise on OA progression.

The same authors embarked on a long-term study to test the hypothesis that intensive weight loss (at least 10% of total body weight), along with exercise, would significantly impact the mechanical and inflammatory pathways of OA. Stephen P. Messier, PhD, Wake Forest University, Winston-Salem, North Carolina, USA, and colleagues launched the Intensive Diet and Exercise for Arthritis [IDEA; NCT00979043] trial, an 18-month study that was designed to evaluate the impact of intensive weight loss, with or without exercise, on disease progression.

A primarily Caucasian, female patient population (n=454) with radiographic knee OA and a mean age of 65 years and body mass index (BMI) of 33.6 kg/m^2 were randomized to one of three arms: (1) intensive dietary restriction alone; (2) intensive dietary restriction plus exercise; or (3) exercise alone. An intention-to-treat analysis was used to compare changes in pain, function, and mobility between groups at 18 months of follow-up.

Eighty-eight percent of patients completed the study. Eighty-five percent of participants had bilateral knee OA. Mean weight loss was 9.5 kg (9.5%) in the dietary restriction-only group, 10.6 kg (11.4%) in the dietary restriction-plus-exercise group, and 2.0 kg (2.2%) in the exercise-only group. None of the participants regressed to her baseline weight during follow-up.

At 18 months, all subjects experienced a decrease in Western Ontario and McMaster University Osteoarthritis (WOMAC) pain scores from baseline. Pain was significantly lower in the dietary restriction-plus-exercise group (51% lower than baseline pain), compared with the 27% reduction in the dietary restriction-only group and 29% reduction in the exercise-only group ($p<0.0004$). The dietary restriction-plus-exercise group also significantly improved ($p=0.003$) on the WOMAC function scale (47% relative to the 30% improvement in the dietary restriction-only group and 24% in the exercise-only group).

All groups demonstrated improvements in walking speed, a measure of mobility. However, walking speed was significantly faster in the dietary restriction-plus-exercise group ($p<0.004$) than either the dietary restriction- or exercise-only group.

"Generally, there is a 1% to 2% decrease in walking speed per decade up to age 62," said Dr. Messier. "When a 12% to 16% decline occurs, it is unexpected." In contrast, the intensive dietary restriction-plus-exercise cohort increased their walking speed by 12%, for a walking speed that was faster than that of healthy women aged 40 to 62 years and equivalent to that of healthy middle-aged men. The study cohort reversed the trend of declining mobility that is seen in older adults. Pain can be significantly reduced and mobility and function improved with long-term, intensive dietary restriction and moderate exercise.

Genome-Wide Analysis of Imputed Genotypes Identifies CCR1/CCR3 As Novel Risk Locus in Behçet Disease

Written by Rita Buckley

Behçet disease (BD) is a genetically complex condition that is characterized by recurrent inflammatory attacks that affect the orogenital mucosa, eyes, and skin. Earlier genomewide association studies (GWAS) have linked the *IL10* and *IL23R-IL12RB2* loci to BD susceptibility [Remmers EF et al. *Nat Genet* 2010; Mizuki N et al. *Nat Genet* 2010]. Yohei Kirino, PhD, National Institutes of Health, Bethesda, Maryland, USA presented the findings of a GWAS analysis of imputed genotypes that are associated with BD.

According to Dr. Kirino, whole-genome imputation was used to identify additional BD susceptibility loci using 96 healthy Turkish controls who were genotyped on Illumina HumanOmni1M-Quad single-nucleotide polymorphism (SNP) chips as a reference. Imputation was conducted using MACH v1.0.15, providing 814,474 SNPs for analysis in 1215 BD cases and 1278 healthy controls. Sequenom iPLEX assays were used to validate the imputation results and to fine map the associated region. Two independent replication sets were genotyped for the most significant SNP.

A p-value cutoff of $1x10^{-5}$ identified 114 non-HLA gene SNPs that were suggestive of association with BD. One imputed SNP, rs7616215 on chromosome 3, located approximately 38 kb from the 3' UTR of the chemokine receptor-1 gene (*CCR1*) (OR, 0.71; $p=1.9x10^{-8}$), exceeded genomewide significance ($p<5x10^{-8}$). Fine mapping of the *CCR1/CCR3* locus confirmed the imputation results for rs7616215 and identified 2 additional SNPs in strong linkage disequilibrium with rs7616215. They also exceeded genomewide significance.

The association of rs7616215 was replicated using additional Turkish and Japanese BD cases and controls in a meta-analysis of 2195 cases and 2187 controls (OR= 0.73; 95% CI, 0.66 to 0.81; $p=1.8x10^{-10}$).

CCR1 belongs to the family of CC-motif chemokine receptors. It is expressed on neutrophils, monocytes, and T lymphocytes and binds several chemokine ligands, including CCL5/RANTES, CCL3/MIP-1α, and CCL4/MIP-1β. Serum levels of *CCRI* ligands, the chemokines MIP-α and RANTES, are increased in BD [Kim SK et al. *Scan J Rhematol* 2005; Ozer HT et al. *Rheumatol Int* 2005].

ENCODE data suggest that the CCRI variant could affect transcription of CCR1/CCR3 and that rs7616215 resides in a putative regulatory genomic domain. Analysis of *CCR1* transcripts from the HapMap of European, Chinese, and Japanese subjects shows that the protective minor allele (C) correlates with significantly increased *CCR1* expression ($p<0.03$). In addition, *STAT4* expression is increased in cells with the BD risk allele. *STAT4* is specifically activated by IL-12 and is a critical signaling mediator for the generation of IFN-γ-producing Th1 T cells.

In summary, imputation identified two novel loci, *CCR1/CCR3* and *STAT4,* that were associated with BD. *CCR1* expression and leukocyte chemotaxis are higher in individuals with the protective allele. *STAT4* expression is higher in individuals with the risk allele. These results implicate leukocyte cell migration and Th1 T cells in the pathogenesis of BD.

To date, HLA-B51 has been the most strongly associated known genetic factor in BD [de Menthon M et al. *Arthritis Rheum* 2009]. This study's identification of *CCR1* and *STAT4* as novel gene loci in BD has potential implications in the regulation of inflammatory responses in the context of the disease. Its findings suggest novel therapeutic targets for BD.

PRESERVE Trial: Patients with Moderately Active RA Achieve and Maintain Low Disease Activity and Remission With Anti-TNF Therapy More Successfully Than Those With High Disease Activity

Written by Rita Buckley

Reimbursement and safety concerns have spurred growing interest in strategies that involve treatment dose reduction or discontinuation once subjects achieve adequate response.

Data from the Randomized, Double-Blind Study Comparing the Safety & Efficacy of Once-Weekly Etanercept 50 mg, Etanercept 25 mg, & Placebo in Combination With Methotrexate in Subjects With Active Rheumatoid Arthritis [PRESERVE; NCT00565409] show that patients with moderately active rheumatoid arthritis (RA) achieve and maintain low disease activity and remission with anti-tumor necrosis factor (anti-TNF) therapy more successfully than those with high RA activity [Keystone E et al. *J Rheumatol* 2009].

The PRESERVE trial compared the efficacy and safety of continuing etanercept 50 mg once weekly+methotrexate 50 mg (E50/M), reducing etanercept from 50 mg to 25 mg once weekly+methotrexate 25 mg (E25/M), then withdrawing etanercept and giving placebo once weekly +methotrexate (P/M) over 52 weeks after sustained low disease activity had been induced during 9 months of E50/M treatment. The primary outcome of the randomized double-blind trial was Disease Activity Score (DAS28) over 88 weeks.

Participants were 18 to 70 years of age, with a diagnosis of RA who were currently receiving an optimal dose of oral MTX (at least 15 mg/week) but no more than 25 mg/week for the treatment of RA. Potential subjects were required to have RA at the time of screening.

Those with moderately active RA (DAS28>3.2 and ≤5.1) who achieved DAS28 low disease activity (DAS≤3.2, average from Weeks 12 to 36) or remission (DAS28<2.6) on E5O/M at Week 36 of Period 1 entered the double-blind Period 2. A total of 604 subjects were randomized based on DAS28 low disease activity/remission to E50/M