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

(n=202), E25/M (n=202), or P/M (n=200) for 52 weeks. MTX was maintained at the same dose throughout the trial (15 to 25 mg).

In all, 497 subjects completed Period 2. The percent of subjects maintaining DAS28 low disease activity at Week 88 was significantly higher in the E50/M (82.6%) and E25/M (79.1%) groups compared with the P/M group (42.6%; p<0.0001 vs either etanercept group). Significantly more subjects had a DAS28 score <2.6 at Week 88 on E50/M (66.7%) and E25/M (60.2%) compared with P/M (29.4%; p<0.0001 vs either etanercept group).

Significantly more subjects on E50/M and E25/M achieved SDAI low disease activity and remission, ACR 20/50/70 responses, and a normal HAQ score (≤0.5) compared with P/M (Table 1). There was a significant change in the modified total Sharp score (units/y) from baseline between the E50/M (–0.06) and P/M (0.60; p=0.0259) groups, but not between the E25/M (0.05) and P/M (0.60; p=0.0696) groups, or the E50/M and E25/M (p=0.6737) groups. No significant differences in safety were observed. Among subjects, 35 (5.8%) reported serious adverse events, including 2 deaths (0.3%) in the E50/M group due to pulmonary embolism and septicemia during Period 2.

Table 1. Effects of Different Treatment Regimens.

	% of Subjects Achieving Endpoint at Week 88		
Efficacy Endpoint	**E50/M**	**E25/M**	**P/M**
SDAI LDA[a]	83.6‡	82.1‡	54.3
SDAI (ACR-EULAR) Remission[b]	37.8‡	31.3‡	11.7
ACR 20/50/70 Responses[c]	75.5‡/62.5‡/25.5‡	74.6‡/57.2‡/31.3‡	48.7/25.9/11.2
HAQ ≤0.5	59.7†	53.2*	41.6
mTSS change ≤0.5 units/y[d]	89.1	88.6	82.6

*p<0.05 vs P/M; †p<0.001 vs P/M; ‡p<0.0001 vs P/M; [a]SDAI ≤11; [b]SDAI ≤3.3; [c]20%/50%/70% improvement from Period 1 baseline in tender and swollen joints and in 3 of the following 5: physician global assessment, patient global assessment, visual analog scale, HAQ, and erythrocyte sedimentation rate; [d]modified intent-to-treat population; E50/M=etanercept 50mg once weekly+methotrexate; E25/M=etanercept 25 mg once weekly+ methotrexate; P/M=placebo+methotrexate; DASS28=disease activity score in 28 joints; LDA=low disease activity; SDAI=simplified disease activity index; ACR=American College of Rheumatology; HAQ=health assessment questionnaire; mTSS=modified total Sharp score.

PRESERVE, the first trial in adults with moderately active RA despite MTX treatment, evaluated induction of DAS28 low disease activity, as well as clinical, functional, and radiographic outcomes with etanercept full-dose continuation, reduction, or elimination on a background of MTX. Subjects were significantly more likely to successfully maintain DAS28 low disease activity (and other clinical benefits) over 52 weeks with the two etanercept treatment regimens than with a step down to P/M. Further research is needed on the longer term implications of these 52-week observations.

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