# Microarray Pathway Analysis Comparing Baricitinib and Adalimumab in Moderate to Severe Rheumatoid Arthritis Patients, from a Phase 3 Study

Paul Emery[1], Peter C. Taylor[2], Michael Weinblatt[3], Yoshiya Tanaka[4], Edward C. Keystone[5], Ernst R. Dow[6], Richard Higgs[6], William L. Macias[6], Guilherme Rocha[6], Terence P. Rooney[6], Douglas E. Schlichting[6], Steven H. Zuckerman[6] and Iain B. McInnes[7], [1]Leeds MSK Biomed/Chapel Allerton Hospital, Leeds, United Kingdom, [2]NDORMS, University of Oxford, Oxford, United Kingdom, [3]Brigham and Women's Hospital, Boston, MA, [4]The First Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan, [5]University of Toronto, Toronto, ON, Canada, [6]Eli Lilly and Company, Indianapolis, IN, [7]University of Glasgow, Glasgow, United Kingdom

## SESSION INFORMATION

**Date:** Tuesday, November 7, 2017

**Session Title:** Rheumatoid Arthritis – Small Molecules, Biologics and Gene Therapy IV: Pharmacodynamic Markers and Therapeutic Intervention

**Session Type:** ACR Concurrent Abstract Session

**Session Time:** 4:30PM-6:00PM

**Background/Purpose:** In RA-BEAM (NCT01710358), baricitinib (BARI), an oral selective inhibitor of Janus kinase (JAK) 1 and JAK 2, yielded significant improvements in patients (pts) with active RA who had an inadequate response to methotrexate compared to placebo (PBO) or adalimumab (ADA).[1] We analyzed molecular pathways modulated by BARI compared with ADA after 4 and 12 weeks (wks) of treatment relative to PBO.

**Methods:** Pts (N=1307) were randomized 3:3:2 (PBO [switched to BARI after 24 wks], BARI 4 mg once daily, ADA 40 mg every other week) for 52 wks. Total RNA extracted from whole blood collected at baseline (BL), wk 4, and wk 12 was analyzed using the GeneChip Human Transcriptome Array 2.0 (Affymetrix). Probeset level data were summarized to a data-driven transcript level and analyzed using a mixed effects model on a log2 transformed response. Multiplicity was adjusted for by testing both within and between transcripts.

**Results:** Pathway analysis revealed that there was little overlap of the immune pathways modulated by both BARI and ADA at wk 4 with no significant overlap by wk 12 (Table). BARI downregulated JAK/Signal Transducer and Activator of Transcription (STAT) signaling pathways, such as those induced by IFNs, IL-6, GM-CSF, IL-5, and IL-3. Expression of interferon responsive genes (IRGs) was downregulated by BARI and upregulated by ADA. BARI reduced IRGs by 75% at wk 4 in pts that had high IFN gene expression at BL. ADA modulated complement pathways. Of interest, STAT transcripts

were reduced at wk 4 by BARI (STAT1, 2, 3, 5A, 5B, 6); by wk 12 several STATs (STAT 1, 2, 5A) did not differ from PBO. In addition to different pathways being modulated, there were additional differences noted in the number of genes modulated by each treatment (Figure). Using PBO as standard, BARI modulated more genes than ADA at wks 4 and 12; BARI resulted in more gene modulation at wk 12 than at wk 4, whereas ADA gene modulation was similar at wks 4 and 12. In addition, both the numbers and types of genes modulated by BARI diverged further from ADA at wk 12 than at wk 4.

**Conclusion:** While BARI and ADA both showed significant benefits compared to PBO in the RA-BEAM trial,[1] gene expression profiling revealed significant differences between treatments. Notably, BARI and ADA modulated JAK/STAT or complement pathways, respectively, and the drugs had opposite effects on interferons. This analysis indicates that different, and possibly complementary mechanisms of action underlie each targeted therapy.

[1]Taylor et al. *N Engl J Med* 2017;376:652-62

**Table. Most Frequent Immune Pathway Changes at Weeks 4 and 12 of Baricitinib and Adalimumab Treatment**

| | BARI vs. PBO | ADA vs. PBO | BARI and ADA |
|---|---|---|---|
| **Week 4** | • ↓ Immune response: IL-6 signaling pathway via JAK/STAT | • Complement pathways (↑ C2, ↓ C3) | • ↑ Immune response: Role of DAP12 receptors in NK cells |
| | • ↓ Immune response: IL-5 signaling via JAK/STAT | • Immune response: IL-4 responsive genes in type 2 immunity (↓ IL4RA) | • Role of integrins in eosinophil degranulation in asthma |
| | • ↓ Development: PEDF signaling | • Dysregulation of germinal center response in SLE (↑ BAFF) | • ↓ Role of IL-23/T17 pathogenic axis in psoriasis |
| | • ↓ Immune response: Antiviral actions of IFNs | • Rheumatoid arthritis: (↓ MMP8/9) | |
| | • ↓ Immune response: IL-22 signaling pathway | • ↓ NETosis in SLE | |
| **Week 12** | • ↓ Immune response: IL-5 signaling via JAK/STAT | • ↑ Immune response: Antiviral actions of IFNs | (Nothing significant) |
| | • ↓ Immune response: Antiviral actions of IFNs | • Complement pathways (↑ C2, ↓ C3) | |
| | • ↓ Immune response: IL-17 signaling pathways | • ↓ CD8+ Tc1 cells in COPD | |
| | • ↓ Immune response: Role of DAP12 receptors in NK cells | • Interleukin-induced inflammatory response in asthmatic airway fibroblasts | |
| | • ↓ Eosinophil survival in asthma | • Proinflammatory cytokine production by Th17 cells in asthma | |

BAFF=B cell activating factor; DAP=DNAX activation protein; JAK=Janus kinase; IFN=interferon; IL=interleukin; MMP=matrix metalloproteinase; NET=neutrophil extracellular trap; SLE=systemic lupus erythematosus; STAT=signal transducer and activator of transcription; Tc=T cytotoxic; Th=T helper; T17=IL-17-secreting T cells

Figure. Number of Genes Modulated by Baricitinib and Adalimumab at 4 and 12 Weeks of Treatment[a]

[a]Lymphocyte, B cell and natural killer cell covariates included
FDR < 0.05, |FC| > 1.10 (FDR = false discovery rate, FC = fold change)