Longer exposure to anti-TNF therapy was associated with a greater reduction in the risk of CV events, primarily myocardial infarction, unstable angina, and congestive heart failure. Risk reduction was also observed in older patients and in methotrexate-naïve patients. Risk reduction was not observed for cumulative exposure to methotrexate or nonbiologic DMARDs.

Table 1. Findings Support Existing Studies.

Study	Population	Exposure	Outcome Measure	Anti-TNF RR or HR
Greenberg et al.	US patients with RA in CRRNA RA registry	Anti-TNF ± MTX vs other nonbiologic DMARDs	• MI/CVA/ TIA/CV death	0.39*
Ljung et al.	Swedish Rheumatology Register	Anti-TNF vs patients with no exposure to anti-TNF	• Acute coronary syndromes	0.80
Barnabe et al.	Meta-analysis of 11 published observational studies	Anti-TNF vs nonbiologic DMARDs	• MI/CHF/ CVA • MI • CVA	0.46* 0.81* 0.69*
Narango et al.	Multinational cross-sectional cohort of consecutive outpatients with RA	Cumulative exposure to anti-TNF vs other (by year)	• MI/CVA/ angina/ coronary disease/ bypass surgery • MI • CVA	0.64* 0.42* 0.64

*Values are statistically significant at the 5% level; CRRNA=Consortium of Rheumatology Researchers of North America; RA=rheumatoid arthritis; MTX=methotrexate; MI=myocardial infarction; CVA=cerebral vascular accident; TIA=transient ischemic attack; CHF=congestive heart failure; CV=cardiovascular; DMARD=disease modifying antirheumatic drug.

12-Week Results of a Phase 2b Dose-Ranging Study of Baricitinib (LY3009104) in Combination with Traditional DMARDs in Patients with RA

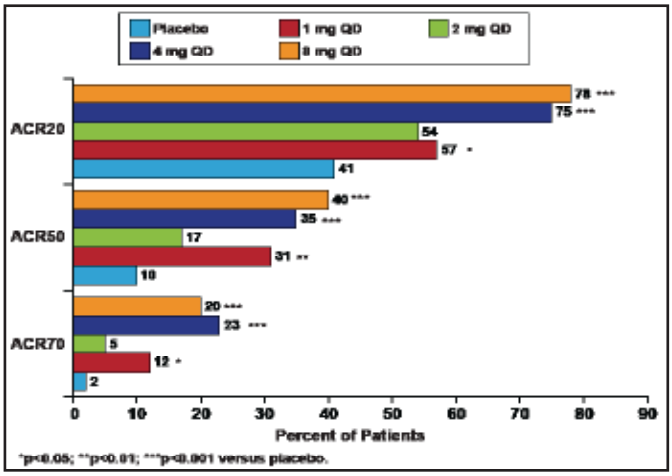
Written by Maria Vinall

Data from a Phase 2b study, presented by Edward Keystone, MD, University of Toronto, Toronto, Ontario, Canada, suggest that baricitinib, an oral JAK1/JAK2 inhibitor, is an efficacious treatment for rheumatoid arthritis (RA) when used in combination with traditional disease-modifying antirheumatic drugs (DMARDs).

JAK tyrosine kinases differentially mediate signal transduction for a variety of cytokines that are involved in inflammatory conditions. JAK1 and JAK2 particularly affect IL-6, IL-12, IL-23, INF-γ, and INF-α/β, suggesting that inhibition of JAK1 or JAK2 would lead to immunomodulation or perhaps immunosuppression. This was a double-blind, placebo-controlled, randomized study to assess the effect of 4 doses of baricitinib, a potent, reversible inhibitor of JAK1 and JAK2, in patients with RA. Eligible subjects had ≥8 swollen and ≥8 tender joints, based on the 66/68 joint count; were on a stable dose of methotrexate for at least 12 weeks or corticosteroids for 6 weeks; and had a maximum C-reactive protein (CRP) level >1.2x the upper limit of normal or an erythrocyte sedimentation rate >28 mm/hr. Subjects were randomized to placebo (n=98) or baricitinib 1, 2, 4, or 8 mg daily (~50 subjects each) in combination with methotrexate and treated for 12 weeks. The primary study endpoint was the ACR20 response at Week 12 for the combined 4- and 8-mg dose groups versus placebo. Major secondary endpoints included ACR20/50/70 and DAS28-CRP response at 12 weeks, safety and tolerability, pharmacokinetics, and patient-reported outcomes.

A total of 301 subjects (mostly women, mean disease duration of ~5.5 years) were enrolled. Subjects in this study had active disease (tender joint count 22/68; swollen joint count 16/66; mean DAS28-CRP score of 5.5; mean Health Assessment Questionnaire [HAQ] score 1.2). At 12 weeks, 76% of subjects who received either 4 or 8 mg of baricitinib achieved the primary endpoint of ACR20 response compared with 41% of placebo-treated patients ($p<0.001$). Treatment with baricitinib also led to significant ($p<0.05$) improvements in ACR20/50/70 at all doses except 2 mg (Figure 1). DAS28-CRP <2.6 response was achieved by 37% of subjects in the 4-mg group and 22% of those in the 8-mg group ($p<0.05$ vs placebo). The onset of efficacy was rapid for ACR20/50/70 and DAS28-CRP, with statistically significant differences seen after 2 weeks of therapy. Simplified Disease Activity Index and Clinical Disease Activity Index remission was achieved more frequently by patients in the 4-mg group (18% and 22%, respectively; both $p<0.05$ vs placebo). Sixty percent of subjects in the 4-mg group and 67% of those in the 8-mg group achieved the minimum clinically important difference for the HAQ-Disability Index compared with placebo (41%) at Week 12.

Figure 1. ACR Responses by Dose at 12 Weeks.



Reproduced with permission from E. Keystone, MD. Keystone et al. *Ann Rheum Dis* 2012;71[Suppl3].

Adverse events (AEs) were mild, and no new safety signals were reported. Dose-dependent decreases in hemoglobin, small increases in serum creatinine, and increases in low- and high-density lipoprotein cholesterol were observed. Seven serious AEs were reported in 6 patients (2 in the placebo group, 3 in the 2-mg group, 1 in the 8-mg group). No deaths or opportunistic infections occurred in the active treatment groups. One patient in the placebo group was diagnosed with an opportunistic infection of toxocariasis. A similar rate of infection was observed in the placebo group (12%) and the combined treatment groups (14%), representing the most common treatment-emergent AE.

Naïve to Biologic Therapy or Inadequate Responders to TNF-α Inhibitors: A Phase 2 Study of LY2439821

Written by Maria Vinall

Evidence from both animal and human models regarding the proinflammatory cytokine interleukin-17 (IL-17) and the T-helper cell (Th17) that secretes it provides a compelling rationale for therapeutic targeting of IL-17 in rheumatoid arthritis (RA). Ixekizumab (LY2439821) is a humanized monoclonal antibody that is used in the treatment of autoimmune diseases [Peck A and Mellins ED. *Infect Immun* 2010; Sarkar S and Fox DA. *Rheum Dis Clin North Am* 2010].

Mark C. Genovese, MD, Stanford University, Palo Alto, California, USA, presented results from an international (75 locations in the United States, Europe, South America, and Asia) Phase 2, 2 Dose-Ranging Study of Multiple Subcutaneous Doses of LY2439821 (an Anti-IL-17 Antibody) in Patients With Active Rheumatoid Arthritis on Concomitant DMARD Therapy [NCT00966875]. Two patient populations were evaluated: biologic disease modifying anti-rheumatic drug [bDMARD]-naïve patients and tumor necrosis factor alpha-inadequate responder [TNFα-IR] patients. To satisfy the TNFα-IR requirement, patients must have been treated with at least one biologic TNFα-inhibitor and had either an insufficient response to at least 3 months of treatment or have been intolerant to treatment, regardless of the treatment duration. All subjects were required to have at least 6 swollen and 6 tender joints and an elevated C-reactive protein (CRP) level. Baseline demographics and clinical characteristics are shown in Table 1.

In this randomized, double-blind study, bDMARD-naïve patients (n=260) received subcutaneous placebo or ixekizumab (3, 10, 30, 80, or 180 mg), and TNFα-IR patients (n=188) received placebo or ixekizumab (80 or 180 mg) at Weeks 0, 1, 2, 4, 6, 8, and 10 with concomitant DMARD therapy. The objectives of the study were to determine the dose-response relationship of ixekizumab in bDMARD-naïve patients, based on the ACR20 response rate (primary) by logistic regression at Week 12. Secondary endpoints included ACR50, ACR70, and ACR20 responders at Week 12 in the TNFα-IR group, Disease Activity Score (DAS) 28 and EULAR28 responses, safety, and tolerability compared with placebo.

"All patients had active disease, significant disability, elevated acute-phase proteins, and fairly high (~6.0) DAS28-CRP scores," Dr. Genovese noted.

There was a significant dose-response relationship in bDMARD-naïve patients at Week 12 (p=0.031 using

Table 1 Baseline Demographics and Clinical Characteristics.

	bDMARD-naïve group						TNFα-IR group		
Parameter (mean)	**Placebo n=54**	**3 mg n=40**	**10 mg n=35**	**30 mg n=37**	**80 mg n=57**	**180 mg n=37**	**Placebo n=64**	**80 mg n=65**	**180 mg n=59**
Women, %	87	83	77	84	91	81	86	88	86
Age, years	53	52	54	53	53	52	53	55	52
Caucasian, %	54	50	60	53	54	60	84	89	85
RF positive, %	74	67	71	68	75	76	75	71	73
ACPA positive, %	76	73	80	81	79	81	64	60	66
BMI, kg/m^2	27	27	29	28	28	27	29.4	28.9	29.3
Disease duration, years	6.1	7.7	7	7.1	6.9	5.8	9.9	13	10.9
Prior use ≥2 biologics, %							50	40	34
Methotrexate dose, mg/week	14	17	15	15	14	15	16	18	16
Prednisone* user	52	48	43	60	51	51	45	55	58
Tender joint count**	15.9	15.1	18.1	15.7	16.8	16.9	15.5	15.3	14.9
Swollen joint count**	11.9	10.7	13.6	11.7	13.9	13.8	12.5	12.6	11.9

No significant difference between groups for any parameter; *prednisone dose was ≤10 mg; ** out of 28; ACPA= anticitrullinated protein antibody; BMI=body mass index; RF=rheumatoid factor.