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.

ACR20; p<0.001 using DAS28-CRP). At Week 12, significant ixekizumab-versus-placebo differences were seen for DAS28 and EULAR28 responses in bDMARD-naïve patients and in TNFα-IR patients for all doses, with a rapid onset of efficacy within 1 week after the first dose and with increasing magnitude of reductions with increasing doses. A rapid onset of clinical efficacy (ACR20, DAS28, and CRP values dropped) occurred within 3 days. Clinical disease activity index (CDAI) responses indicated the effects of ixekizumab extend beyond the acute-phase proteins.

There were no deaths. The frequency of treatment-emergent adverse events (AEs) was similar across treatment arms (range: 45% to 62%). More patients experienced infections in the treatment arms (37% combined) compared with placebo (18%), with no observed dose relationship. Treatment-emergent serious AEs occurred in 2 patients in the placebo group (1.7%) and 16 ixekizumab-treatment patients (4.8%). Upper respiratory tract infection, urinary tract infection, systemic allergic/hypersensitivity reaction, injection-site pain, and headache were the most frequent treatment-emergent AEs in both groups. No mycobacterial or systemic fungal infections were observed. Most patients had grade 1 neutrophil counts through Week 12. The safety profile was comparable with that of other biologic therapies.

"It appears that ixekizumab results in significant improvements in symptoms and signs, in both the biologic DMARD-naïve patients as well as the anti-TNF inadequate-responder groups," Dr. Genovese said.

LITHE Study Subset: Identification of Tocilizumab Early Response-Associated Biomarkers

Written by Rita Buckley

Proteolytic enzymes, such as matrix metalloproteinase (MMP), are unregulated in inflamed tissue. The protein fragments that are generated from MMP-mediated protein destruction are known as neoepitopes, which serve as biomarkers of inflammation in patients with rheumatoid arthritis (RA). The aim of this study, presented by Anne C. Bay-Jensen, MS, PhD, Nordic Bioscience, Harlev, Denmark, was to identify biomarker profiles that are associated with early response to tocilizumab in patients with RA, using neoepitope markers.

The Randomized, Double-Blind Study of Safety and Prevention of Structural Joint Damage During Treatment With Tocilizumab Versus Placebo, in Combination With Methotrexate, in Patients With Moderate to Severe Rheumatoid Arthritis study [LITHE; NCT00106535] examined the efficacy of tocilizumab in a Phase 3, 3-arm, randomized, parallel-group study of 1196 patients with moderate or severe active RA who had inadequate response to methotrexate. This analysis included a subset of patients from the tocilizumab 8 mg/kg plus methotrexate arm (TCZ8; n=206) and from the placebo plus methotrexate arm (n=211). Nonresponders were escape patients from the TCZ8 arm, defined as <20% improvement in both swollen joint count (SJC) and tender joint count (TJC) at Week 16.

The effect of TCZ8 (n=168) versus placebo (n=112) on serum biomarkers was monitored from baseline to Week 52. Patients who were receiving rescue treatment were excluded. An early-response profile was determined by subdividing TCZ8-treated patients into responders (n=91) and nonresponders (n=29). Serum biomarkers were measured, including the inflammation markers' total C-reactive protein (CRP), the neoepitope MMP-degraded CRP (CRPM), and citrullinated and MMP-generated vimentin fragments (VICM); the cartilage degradation and synovium turnover markers MMP3 and the MMP-degraded type II and III collagen (C2M and C3M, respectively); and the bone turnover markers osteocalcin, cathepsin K-mediated type 1 collagen degradation (CTX-I), and MMP-degraded type I collagen (ICTP).

In response to TCZ8, CRP was significantly blocked whereas CRPM continued to decrease over time (p<0.0001 for both at Weeks 4 and 52). TCZ8 significantly inhibited C2M (p<0.001 at Week 4; p<0.01 at Week 52) and C3M (p<0.0001 at Weeks 4 and 52) levels compared with baseline. From baseline, the mean % change in CRPM (responders, about -24% vs nonresponders, about -60%; OR, 4.0; 95% CI, 1.7 to 9.4; p=0.0014), but not in CRP (responders, about -64% vs nonresponders, about -14%; OR, 1.6; p=0.18), at 4 weeks was predictive of TCZ8 response. The mean % change from baseline in C2M (responders, about -10% vs nonresponders, about +10%; OR, 5.8; 95% CI, 2.2 to 15; p=0.0003) and in C3M (responders, about -23% vs nonresponders, about -10%; OR, 9.6; 95% CI, 2.8 to 33; p=0.0004) was highly predictive of TCZ8 response.

TCZ8 strongly inhibited markers of cartilage degradation (C2M) and inflammation-mediated tissue turnover (C3M, CRPM), which may explain, in part, the beneficial effect of TCZ on the joints. In contrast to traditional CRP and the other markers that were measured, the novel neoepitope biomarkers of cartilage and synovial turnover discriminated between early TCZ8 responders and nonresponders. These neoepitope markers may reflect the same predictive effect with other doses of TCZ or other biologic interventions.