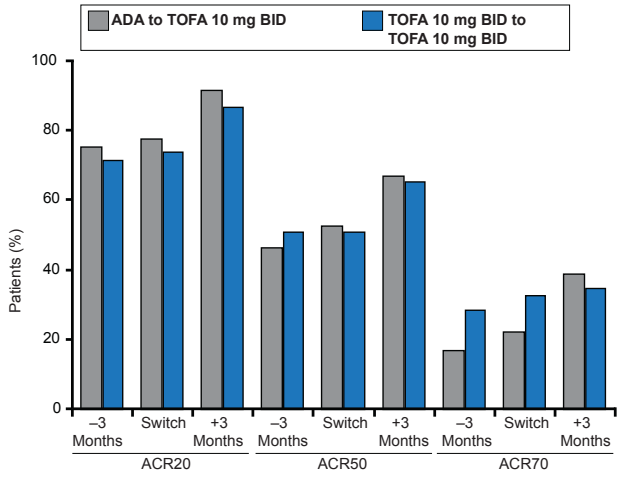
numerically similar to ADA 40 mg Q2W on three primary outcome measures: 20% improvement at Month 6 in the American College of Rheumatology scale (ACR20); the change from baseline to Month 3 in the score on the Health Assessment Questionnaire-Disability Index (HAQ-DI); and the percentage of patients at Month 6 who had a Disease Activity Score for 28-joint counts based on the erythrocyte sedimentation rate (DAS28-4[ESR]) of <2.6 [van Vollenhoven RF et al. *N Engl J Med* 2012].

Subjects who completed ORAL Standard were eligible to enroll in ORAL Sequel, receiving TOFA 10 mg BID, without a washout, with the timing of the first TOFA dose ≤1 week following the last dose of ADA in ORAL Standard. The goal was to define the efficacy and safety of transitioning from ADA to TOFA without a washout.

Of the 204 subjects randomized to ADA, 145 enrolled in ORAL Sequel and 125 of them began TOFA without a washout ≤1 week after their last dose of ADA in Oral Standard. Of the 201 subjects randomized to TOFA, 148 enrolled in ORAL Sequel and 124 took their first dose of TOFA ≤1 week after their last dose of TOFA in Oral Standard.

Results were reported for subjects randomized to ADA 3 months before the end of ORAL Standard, at the end of ORAL Standard, and 3 months after the transition to TOFA in ORAL Sequel. Data for TOFA 10 mg BID, during each phase were reported for the same time points. The ACR20 response rate in patients randomized to ADA were 74.2% at 3 months before the end of ORAL Standard, 76.6% at the end, and 90.5% at 3 months after the transition to TOFA in ORAL Sequel. A similar pattern was observed for ACR50 and ACR70 responses (Figure 1).

Figure 1. Efficacy: ACR Responses in Last 3 Months of ORAL Standard and First 3 Months of ORAL Sequel Study



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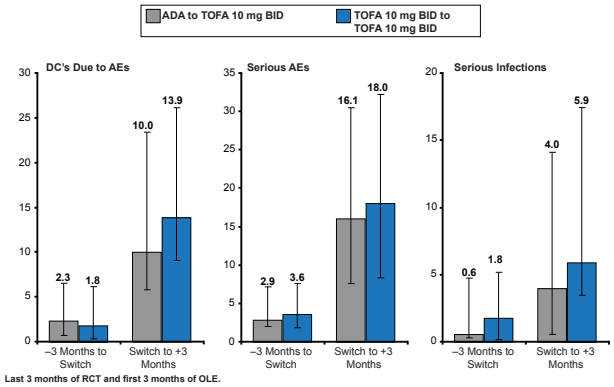
Mean change from baseline in HAQ-DI in patients transitioning from ADA to TOFA was -0.55, -0.60, and -0.70 at these same three time points. Efficacy results in patients who continued on TOFA were similar at the same time points and showed a similar pattern of increases from ORAL Standard to ORAL Sequel. The rate of serious adverse events increased post transition in both groups, when analyzed per 100 patient-years (Figure 2). The overlapping immunomodulatory effects of ADA and TOFA did not appear to be the cause of the increase in safety-related events, because they were increased in both groups.

Figure 2. Safety: Incidence Rates per 100 Patient-Years



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MOBILITY Part A Hones in on Effective Dosing for Sarilumab in RA

Written by **Larry Hand**

Rheumatoid arthritis (RA) patients treated with sarilumab (SAR) 150 or 200 mg Q2W or 100 or 150 mg QW were more than twice as likely to achieve an American College of Rheumatology 50 (ACR50) response after 12 weeks, compared with patients treated with placebo, and the benefit started appearing as early as 2 weeks. Roy Fleischmann, MD, Metroplex Clinical Research Center, Dallas, Texas, USA, presented a poster of a post hoc analysis from the Evaluation of SAR153191 (REGN88; Sarilumab) on Top of Methotrexate in Rheumatoid Arthritis Patients study [RA-MOBILITY; NCT01061736; Fleischmann R et al. EULAR 2013 (poster 0136)].

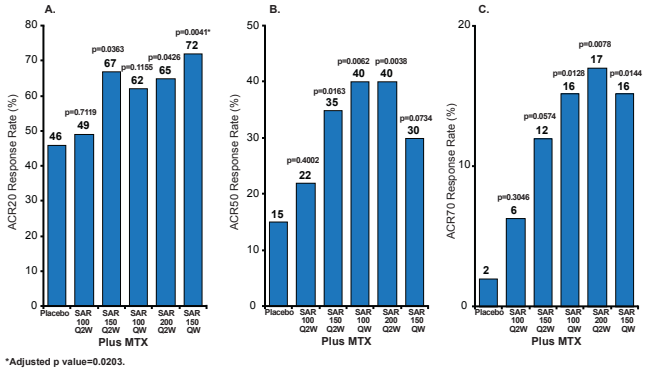
The need for new therapies is known, with only a minority of RA patients achieving a sustained clinical remission, despite the current treatment options [Kavanaugh A et al. *Ann Rheum Dis* 2013]. It has been shown that an elevated level of interleukin 6 (IL-6) drives inflammation in RA [Srirangan S,

Choy EH. *Ther Adv Musculoskelet Dis* 2010], and work by a number of investigators has shown that blocking IL-6α with monoclonal antibodies (mABs) has been effective for some patients. A reduction in acute phase reactants has been shown with mABs in Phase I studies [Radin A et al. *Arthritis Rheum* 2010; Radin A et al. *Ann Rheum Dis* 2010].

This post hoc analysis was performed to evaluate the time-to-event of key outcomes by assessing differences in temporal patterns of the cumulative incidence of ACR20, ACR50, ACR70, and European League Against Rheumatology (EULAR) good plus moderate responses. A total of 306 adult patients with active RA for at least 3 months and with an inadequate response to methotrexate (MTX) in the Mobility Part A dose ranging study were included in this analysis. Baseline patient characteristics were similar among all groups (mean age at 52.2 years, 93.9% Caucasian, 79% women, mean disease duration of 7.8 years, and rheumatoid factor positivity 79.7%).

Researchers randomized the patients into 6 arms (n=51 or 52 each) to receive either SAR 100 mg Q2W plus MTX; SAR 150 mg Q2W plus MTX; SAR 100 mg QW plus MTX; SAR 200 mg Q2W plus MTX; SAR 150 mg QW plus MTX; or placebo plus MTX. All drug administration was subcutaneous. Figure 1 details the key results, including the primary endpoint of the ACR20 response rate at 12 weeks.

Figure 1. Primary and Secondary Outcomes (ACR Responses at Week 12)



ACR=American College of Rheumatology; Q2W=every other week; QW=weekly; SAR=sarilumab.

SAR doses of 150 mg Q2W or higher reduced RA signs and symptoms. Relative hazard ratios (HRs) favored 4 out of the 5 SAR doses compared with placebo, but not for 100 mg Q2W (Table 1). One death occurred from respiratory distress syndrome or a cerebrovascular accident in the SAR 100 mg Q2W group. Six of the 8 patients who experienced treatment-related adverse events in the two SAR groups discontinued treatment.

Table 1. Likelihood of Achieving Efficacy Outcome With Sarilumab Compared With Placebo

Placebo, n=52 (Reference arm)	n	Relative Hazard (95% CI)	p Value
ACR20			
100 mg Q2W	51	1.07 (0.66–1.75)	0.7816
150 mg Q2W	51	1.43 (0.89–2.30)	0.1378
100 mg QW	50	1.31 (0.80–2.12)	0.2815
200 mg Q2W	52	1.51 (0.95–2.41)	0.0848
150 mg QW	50	1.50 (0.93–2.41)	0.0939
ACR50			
100 mg Q2W	51	1.06 (0.45–2.46)	0.9
150 mg Q2W	51	2.15 (1.06–4.63)	0.04
100 mg QW	50	2.51 (1.25–5.36)	0.01
200 mg Q2W	52	3 (1.53–6.32)	<0.01
150 mg QW	50	2.19 (1.07–4.73)	0.04
ACR70			
100 mg Q2W	51	2.09 (0.38–11.39)	0.3957
150 mg Q2W	51	4.27 (0.91–20.10)	0.0664
100 mg QW	50	6.13 (1.36–27.66)	0.0183
200 mg Q2W	52	5.19 (1.14–23.70)	0.0335
150 mg QW	50	6.40 (1.42–28.88)	0.0157
EULAR (Good/Moderate)			
100 mg Q2W	51	1.12 (0.72–1.75)	0.6209
150 mg Q2W	51	1.79 (1.16–2.76)	0.0082
100 mg QW	49	2 (1.30–3.11)	0.0017
200 mg Q2W	50	2.05 (1.34–3.18)	0.0011
150 mg QW	50	1.99 (1.28–3.09)	0.0021

ACR=American College of Rheumatology; EULAR=European League Against Rheumatism; Q2W=every other week; QW=weekly.

The likelihood of achieving efficacy with an ACR50 response was high in 4 of 5 SAR doses but fell short for ACR20 responses.

Lower-Dose Etanercept Plus Methotrexate Shows Benefit for Early RA Patients in PRIZE Trial

Written by **Larry Hand**

In patient-reported outcomes for those with recently diagnosed rheumatoid arthritis (RA), treatment with etanercept 25 mg (ETN25) plus methotrexate (MTX) was superior to MTX plus placebo or placebo alone in maintenance of remission and therapeutic effect. Paul Emery, MD, University of Leeds, Leeds, United Kingdom, presented a poster of the results of A 3-Phase Study to Evaluate Sustained Remission and Productivity Outcomes in Subjects With Early Rheumatoid Arthritis Initiated on Treatment With Etanercept Plus Methotrexate [PRIZE;