The percentage of responders using the more stringent SRI-6 was also higher at all doses of sifalimumab (placebo, 37.4%; 200 mg, 50.0%; 600 mg, 43.5%; 1200 mg, 53.3%). The effect size for response vs placebo was 12.6% with 200 mg ($P = .051$), 6.1% with 600 mg ($P = .301$), and 15.9% with 1200 mg ($P = .016$).

The British Isles Lupus Assessment Group–based Combined Lupus Assessment response at week 52 was also higher in patients randomized to sifalimumab compared with placebo (placebo, 36.1%; 200 mg, 45.4%; 600 mg, 46.7%; 1200 mg, 48.1%).

A Cutaneous Lupus Erythematosus Disease Area and Severity Index response (≥ 4-point reduction from baseline) in patients with moderate to severe skin involvement was achieved by more patients randomized to sifalimumab compared with placebo (placebo, 48.6%; 200 mg, 72.7%; 600 mg, 57.6%; 1200 mg, 73.1%).

The number of patients with ≥ 8 swollen and ≥ 8 tender joints at baseline who achieved a ≥ 50% decrease in swollen and tender joint count was an exploratory end point. On this measure, the response rate is higher at all doses of sifalimumab (placebo, 36.8%; 200 mg, 53.7%; 600 mg, 57.9%; 1200 mg, 60.5%).

Response rates on the SRI-4 were higher than placebo with sifalimumab regardless of high or low IFN gene signatures.

Most commonly reported adverse events (AEs) were similar across groups, including worsening SLE (sifalimumab 30.0% vs placebo 34.3%), urinary tract infection (17.6% vs 13.9%), and headache (13.3% vs 13.9%). Serious AEs occurred in 18.3% of the sifalimumab group vs 17.6% of the placebo group. Herpes zoster infection was more common in sifalimumab recipients vs placebo (5.9% vs 0.9%).

The overall efficacy results suggest that 1200 mg monthly is the most efficacious dose of sifalimumab for use in moderate to severe SLE.

## GR Agonist Improves Responses in RA

Written by Wayne Kuznar

Response rates with an investigational dissociated agonist of the glucocorticoid receptor (DAGR) were comparable with response rates with prednisone in patients with rheumatoid arthritis (RA). Results of a phase 2 trial were presented by Vibeke Strand, MD, Stanford University, Stanford, California, USA.

The glucocorticoid receptor (GR) regulates genes that control development and metabolism and the immune response [Buttgereit F et al. *Lancet.* 2005; *Arthritis Rheum.* 2004]. A DAGR is a nonsteroidal ligand of the GR that has both partial agonist and antagonistic properties [De Bosscher K et al. *Brain Behav Immun.* 2010].

Preclinical and phase 1 and phase 2a clinical data had demonstrated that PF-04171327, a selective high-affinity partial agonist of the GR, possesses potent anti-inflammatory activity at doses that produce potentially fewer adverse effects commonly associated with glucocorticoids, namely adverse bone and glucose metabolism [Hu X et al. *Endocrinology.* 2011].

The phase 2 trial was undertaken to determine the efficacy and safety of 4 doses of DAGR after 8 weeks of treatment compared with placebo and prednisone. It was conducted in 323 patients who had moderate to severe RA despite treatment with methotrexate. Patients were randomized to receive once-daily doses of the DAGR at 1, 5, 10, or 15 mg; prednisone, 5 or 10 mg; or placebo for 8 weeks, followed by a 4-week taper.

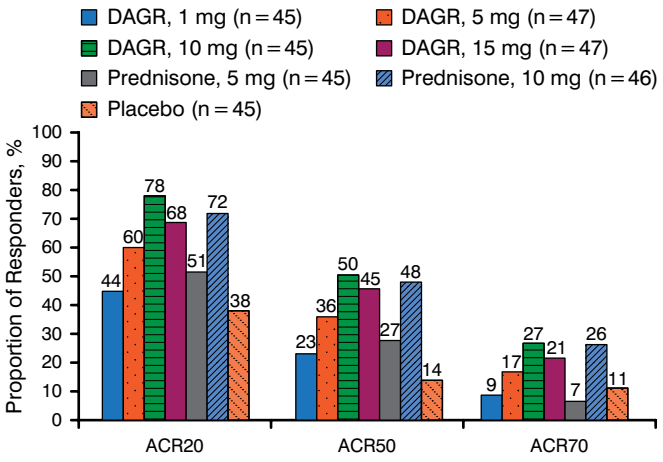
The primary end points at week 8 were American College of Rheumatology 20% improvement response criteria (ACR20) and assessment of the dissociation bone biomarkers total procollagen type 1 N-terminal propeptide (P1NP) and osteocalcin, markers of bone formation, and urine N-telopeptide/urine creatinine (uNTX/uCr) and serum C-telopeptide, markers of bone resorption.

ACR20 responses were achieved by 78% of patients randomized to 10 mg/d of DAGR. The proportion of responders to other doses of DAGR ranged from 44% (1 mg) to 68% (15 mg). Among patients randomized to prednisone, 51% achieved an ACR20 response with 5 mg and 72% with 10 mg. Thirty-eight percent of the placebo group had an ACR20 response. The rates of ACR50 and ACR70 responses were also similar between DAGR and prednisone (Figure 1). DAGR 10 and 15 mg were significantly superior to placebo, and DAGR 15 mg was noninferior to prednisone 10 mg.

Compared with prednisone 5 mg, the 1-, 5-, and 10-mg doses of DAGR were noninferior on P1NP values, and all doses of DAGR were noninferior on the osteocalcin end point. Compared with prednisone 5 mg, DAGR at 1, 5, and 10 mg was noninferior on the uNTX/uCr end point, and 5 mg of DAGR was noninferior on serum C-telopeptide. All doses of DAGR and 5 mg of prednisone resulted in similarly small decreases in $HbA_{1c}$ values from screening to week 8.

The safety profile of DAGR was comparable with placebo and prednisone. The rates of treatment-emergent adverse events (AEs) were similar across all groups. Serious AEs occurred in 2% to 4% of patients in each randomized group. No significant laboratory abnormalities were observed. Suppression of plasma cortisol was observed with 5, 10, and 15 mg of DAGR compared with

Figure 1. ACR20/50/70 Responses at Week 8 With DAGR, Prednisone, and Placebo




ACR20/50/70, American College of Rheumatology 20%/50%/70% improvement response criteria; DAGR, dissociated agonist of the glucocorticoid receptor.

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partial suppression with prednisone at 5 and 10 mg. No clinical symptoms of adrenal insufficiency were reported at any time. Prompt recovery of the hypothalamic-pituitary-adrenal axis was evident at week 13 in all patients.

The totality of the data demonstrates superior efficacy of DAGR 10 and 15 mg compared with placebo and comparable efficacy compared with prednisone 10 mg, concluded Dr Strand. All DAGR doses were noninferior to prednisone 5 mg on bone formation biomarkers.

## Preventing GC-Induced Bone Loss in Women With RA

Written by Jill Shuman

Glucocorticoids (GCs) are a commonly prescribed treatment for patients with rheumatoid arthritis (RA). However, the long-term use of these agents in postmenopausal women is associated with an increased risk of osteoporosis and fracture. Therefore, the prevention of GC-induced osteoporosis has become an important goal in treating women with RA.

Kichul Shin, MD, PhD, Seoul Metropolitan Government–Seoul National University Boramae Medical Center, Seoul, South Korea, presented data from the now complete randomized, double-blind phase 4 clinical trial, Efficacy of Monthly Ibandronate in Women With RA and Reduced Bone Mineral Density Receiving Long-Term Steroids [NCT01287533]. Ibandronate is a bisphosphonate currently approved for the prevention and treatment of women with osteoporosis, but little is known about its potential to prevent GC-induced osteoporosis. Therefore, this study was designed to determine if administration of oral ibandronate once per month would be effective in preventing GC-induced osteoporosis in women with RA and reduced bone mineral density (BMD).

The study included 167 women with RA from 13 centers in South Korea who were randomized to receive either oral ibandronate 150 mg every 4 weeks (n = 86) or placebo (n = 81). All women had been taking GCs for at least 3 months prior to enrollment and had L1-4 T-scores of < –1.0 to –2.5 or higher as measured by dual-energy x-ray absorptiometry (DEXA). The women received 1500 mg of calcium carbonate daily as well as cholecalciferol 400 IU. The mean age of the women was 54.49 years in the ibandronate group and 55.11 years in the placebo group; the majority of women in either group did not smoke, drink alcohol, or have a family history of osteoporosis. The average duration of GC use was 2 years with an average cumulative dose of about 50 g.

The primary outcome measure was the percent change of the L1-4 T score at 48 weeks from baseline. Other outcome measures included L1-4 BMD changes at 48 weeks compared with baseline, incidence of fracture in both groups, and the presence of any safety signals. The primary outcome measure was assessed at 48 weeks as both a modified intention-to-treat (mITT) analysis (n = 149) and a per-protocol (PP) analysis (n = 116).

DEXA measurement showed a significant reduction in percentage of bone loss among the women who received ibandronate in both the mITT and the PP analyses ($P = .0001$, both). As well, there were significant L1-4 BMD reductions at 48 weeks compared with placebo in both the mITT and PP analyses ($P = .0001$, both). Importantly, there was no incidence of fracture in either the ibandronate or the placebo groups. Safety profiles, including adverse events such as gastrointestinal, cardiac, and vascular disorders, were comparable between the 2 groups.

In conclusion, monthly oral administration of the bisphosphonate ibandronate significantly reduced bone loss and increased BMD in women with RA on long-term GCs. These data suggest the need for longer follow-up studies to assess whether ibandronate is an appropriate long-term treatment for preventing GC-induced osteoporosis.