Sifalimumab Slows Disease Activity in SLE

Written by Wayne Kuznar

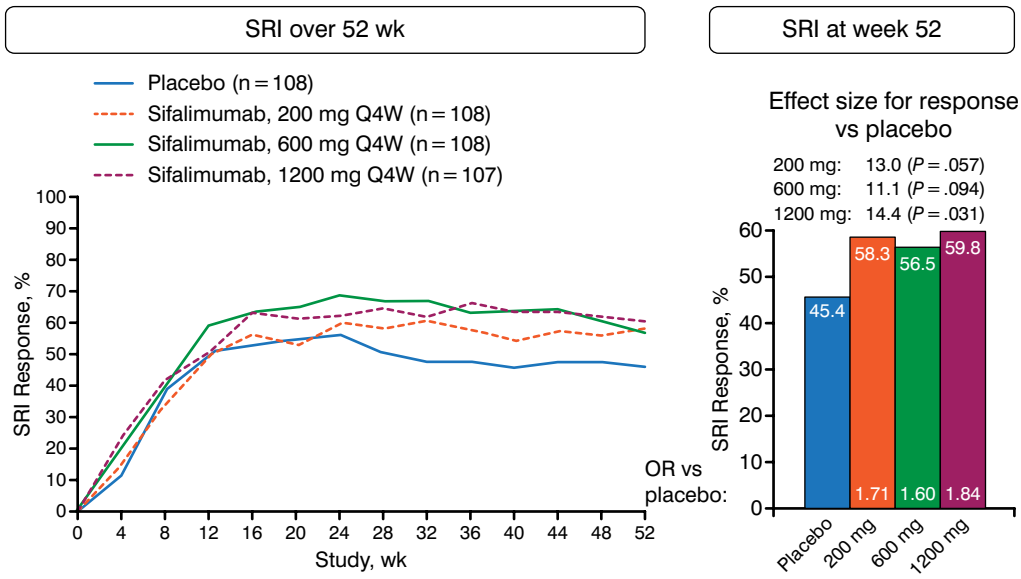
An investigational anti–interferon (IFN)-α monoclonal antibody, sifalimumab, reduced global disease activity in patients with systemic lupus erythematosus (SLE). Munther Khamashta, MD, St Thomas' Hospital, London, United Kingdom, presented results from a phase 2b study of sifalimumab in patients with moderate to severe SLE.

Type I IFNs play a key role in the pathogenesis of SLE [Crow MK. *J Immunol.* 2014; Elkon KB, Wiedman A. *Curr Opin Rheumatol.* 2012; Elkon KB, Stone VV. *J Interferon Cytokine Res.* 2011; Rönnblom L et al. *Semin Immunol.* 2011; Dall'era MC et al. *Ann Rhuem Dis.* 2005]. Type I IFNs activate multiple pathways central to SLE pathogenesis [Kirou KA et al. *Arthritis Rheum.* 2005], including activation of monocytes, dendritic cells, neutrophils, T cells, and B cells. IFN-α is the predominant subtype of type I IFNs [Hillyer P et al. *Immunol Cell Biol.* 2012]. Sifalimumab is a fully human monoclonal antibody binding and neutralizing the majority of IFN-α subtypes [Merrill JT et al. *Ann Rheum Dis.* 2011].

The study included 431 adults with moderate to severe SLE and with a SLE Disease Activity Index 2000 ≥6 and a Physician's Global Assessment ≥1.0 at screening. Patients were receiving standard-of-care treatment at the time that they were randomized to placebo or 1 of 3 monthly doses of sifalimumab administered intravenously: 200, 600, or 1200 mg. The primary end point was the percentage of patients that responded as measured by the Systemic Lupus Erythematosus Responder Index (SRI) at week 52. Approximately 85% of the patients in each randomized group completed the study.

The percentage of patients that achieved an SRI-4 response at week 52 was higher for sifalimumab at all doses vs placebo (Figure 1). The effect size for response vs placebo was 13.0% with 200 mg (P=.057), 11.1% with 600 mg (P=.094), and 14.4% with 1200 mg (P=.031).

Figure 1. Primary End Point: SRI Response



OR, odds ratio; Q4W, every 4 weeks; SRI, Systemic Lupus Erythematosus Responder Index.

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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