study in which greater efficacy was seen with abatacept, but not TNF inhibitors, in anti-CCP2+ vs anti-CCP2- pts with RA (Harrold et al. J Rheumatol.2018).

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Methods: The MR was implanted in 14 patients with active RA and prior insufficient response to ≥2 bDMARDs or JAK inhibitors with ≥2 different modes of action; all patients remained on stable background of methotrexate. Three weeks after implantation, the first 3 subjects were stimulated 1 min QD and, following safety review board approval, the remaining 11 patients were implanted with the MR and randomized to 1 min of sham, QD, or QID stimulations for 12 weeks. Patients, rheumatologists, joint assessors and monitors were fully blinded to treatment arm. Subjects randomized to sham had their devices activated after the primary endpoint at 12 weeks. Clinical efficacy was measured by DAS28-CRP response and contrast-enhanced MRI (RAMRIS OMERACT). The pharmacodynamic response to VNS was assessed in blood using cytokine production in an ex-vivo bioassay (TruCulture).

Results: 14 patients were enrolled (mean prior bDMARDS= 4.8, mean DAS28-CRP= 5.94). Implantation and stimulation were generally well tolerated. There were no device or treatment-related SAEs and 2 surgery related adverse events (left vocal cord paralysis, Horner’s syndrome) that resolved with no clinically significant sequelae. DAS28-CRP change at week 12 was (mean ± SEM): Open label QD = -1.44 ± 0.64, QD = -1.24 ± 0.88, QID= 0.38 ± 0.71, Sham= 0.16 ± 0.21. Of QD stimulated patients, 4 of 6 had a EULAR good or moderate response. Measures of synovitis or osteitis did not change after 12 weeks of stimulation. RAMRIS erosion scores correlated with EULAR response (change ± SEM in erosion scores in EULAR responders = -2.2 ± 1.4 vs. 2.4 ± 0.96 in EULAR non-responders). The pharmacodynamic response to VNS was confirmed in actively stimulated groups with >30% decrease from baseline in bioassay levels of IL-1β, IL-6, and TNF-a at week 12.

Conclusion: The novel MR device and stimulation was well tolerated independently of the two surgery-related events. MR associated stimulation reduced signs and symptoms of RA in a meaningful number of highly drug-refractory subjects. No clinical improvement was observed in the sham group. These initial pilot data support the use of the MR in a larger blinded sham-controlled study in patients who have failed biologics or targeted oral therapies as a novel approach for treatment of RA and other chronic inflammatory diseases. 

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