

ABSTRACT NUMBER: 1439

Lymphatic Delivery of Etanercept Achieves Significant Improvements in Rheumatoid Arthritis Disease Measures at 50% of the Standard Dose for Patients with an Inadequate Response to Subcutaneous Injections

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Meeting: ACR Convergence 2022**Keywords: Anti-TNF Drugs, clinical trial, rheumatoid arthritis**

SESSION INFORMATION

Date: Sunday, November 13, 2022**Session Type:** Poster Session C**Session Title: RA – Treatment Poster III****Session Time:** 1:00PM-3:00PM

Background/Purpose: The lymphatic system plays an integral role in the pathology of rheumatoid arthritis (RA)¹ and mediates local RA flares², yet most biologic therapies are dosed subcutaneously (SC) or intravenously (IV). Nanotopography-microneedles (NTM) have previously been shown to enhance local lymphatic delivery and improve therapeutic efficacy in collagen-induced arthritic rats³. Here we report interim results from a 10-patient Phase 1b clinical trial in patients with high to moderate RA activity and with a history of an inadequate response to weekly SC injections of 50 mg of etanercept who were switched to weekly NTM-device-facilitated lymphatic delivery of 25 mg of etanercept for 12 weeks.

Methods: The NTM device was applied to the dorsal forearm and etanercept infused for 1.25 hours. The device was alternately applied between the left and right forearms every other week. Lymphatic imaging was conducted using Near-Infrared Fluorescence (NIRF) imaging techniques with indocyanine green dye³ to evaluate delivery into the lymphatic vessels and draining axillary lymph nodes, and to determine if lymphatic function (pump rates) improved after treatment. Data from the first 7 patients enrolled are included in this analysis. The patient baseline demographics and disease characteristics are given in Table 1. The remaining 3 patients are currently completing 12 weeks of dosing.

Results: Switching from once weekly 50 mg SC injections to once weekly 25 mg lymphatic delivery significantly reduced disease activity without local adverse events or drug delivery-related immune responses. Patients with high DAS28(CRP) baseline scores were reduced to moderate levels and patients with moderate DAS28(CRP) baseline scores were reduced to low disease activity levels (Figure 1A). Patient Global Assessment of Disease Activity and Patient Disease Pain concomitantly

decreased (Figure 1B). Lymphatic function, based on average pump rates, increased from a baseline of 1.0 to 2.9 pumps/minute after 12 weeks of treatment (Figure 2).

Conclusion: The NTM device effectively delivers lymphatically based on NIRF imaging results. RA disease activity and lymphatic function were improved in all patients. These improvements resulting from use of the NTM device underscore the importance of directing TNF α inhibitors locoregionally to lymphatics and lymph nodes in the treatment of RA.

1. Yousef, M et al.: J Pharm Pharm Sci 2021; 24: 533-47 (ww.capsCanada.org)
2. Rahimi, H et al.: Arth Res Ther 2016; 18:194-203
3. Aldrich, MB et al.: Arth Res Ther 2017; 19:1-13

Patient Baseline Demographics and Disease Characteristics							
Patient ID	Age	Sex	Disease Duration	Duration on Etanercept	Other RA Medications	Comorbidities	Disease State at Baseline-DAS28(CRP)
Patient 1	43	Female	2 years	10 months	Methotrexate, Prednisone, Folic Acid	Hypertension, Obesity, Type 2 DM, GERD, CAD	High (5.0)
Patient 2	69	Male	6 years	16 months	Hydroxychloroquine	Type 2 DM, Cervical Spondylosis, Hypothyroidism, Cervical & Lumbar Spondylosis, GERD	Moderate (4.4)
Patient 3	51	Female	2 years	26 months	Methotrexate, Folic Acid	Venous Reflux Disease LEs	High (5.3)
Patient 4	52	Female	10 years	6 months	Hydroxychloroquine, Prednisone, Naproxen	Osteopenia, Narcolepsy, Migraine, GERD, Thyroiditis	High (6.1)
Patient 5	47	Female	4 years	9 months	Leflunomide, Hydroxychloroquine, Ibuprofen, Diclofenac	HSV 1, HSV 2, Osteopenia, Migraine, GERD, Essential Tremors	High (6.1)
Patient 6	56	Female	2 years	6 months	Acetaminophen, Hydrocodone	Hypertension, Hypercholesterolemia, Hypothyroidism, Insomnia	High (4.8)
Patient 7	57	Female	12 years	11 years	Methotrexate, Sulfasalazine, Prednisone, Ibuprofen, Diclofenac	Scoliosis, Osteopenia, Pulmonary Granuloma, Dupuytren's Contracture	High (5.7)

Table 1: Baseline demographics and disease characteristics for first 7 patients. "Other RA Medications" column includes additional therapies patients were using at W0 (baseline) to treat RA; "Comorbidities" column includes ongoing medical conditions at W0; "Disease State" column represents disease activity at W0 (baseline), as measured by DAS28(CRP).

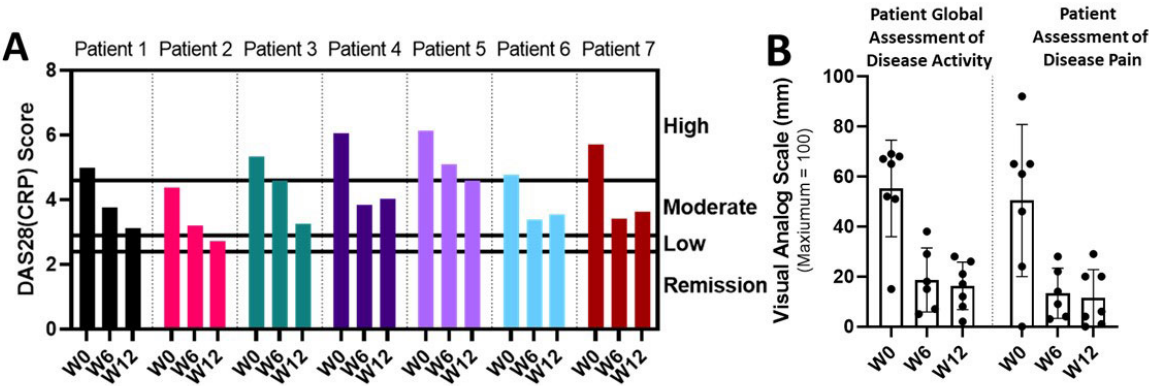


Figure 1: Disease scoring and metrics in patients treated using lymphatic delivery of etanercept. A) DAS28(CRP) levels at W0 (baseline), W6, and W12, and B) Left) Patient Global Assessment of Disease Activity, Right) Patient Assessment of Disease Pain. Data are represented as mean ± SE (SE is the standard error).

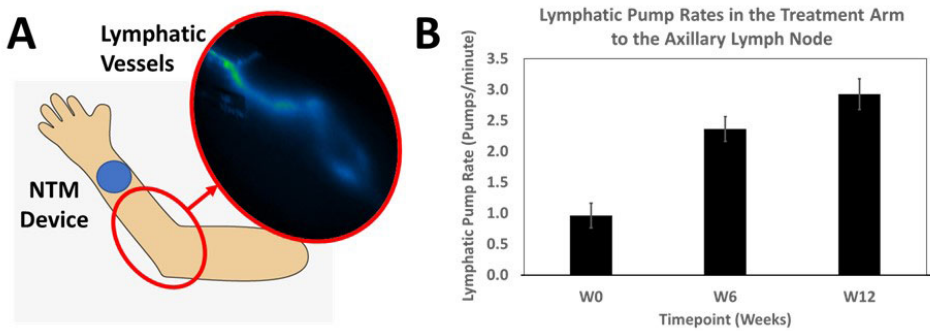


Figure 2: Improvements in lymphatic function from week 0 (W0) to 12 (W12) from lymphatic delivery of etanercept. A) Shows the nanotopography-microneedle (NTM) device dosing location on the patient and where the lymphatic vessels were imaged with indocyanine green dye. B) Comparison of lymphatic pump rates at W0 (baseline), 6 weeks (W6) and 12 weeks (W12) dosing. Data is presented as mean ± SE (SE is the standard error).

Disclosures: **A. Smith**, Sorrento Therapeutics; **P. Roerig**, None; **J. Cason**, Sorrento Therapeutics; **D. Fancis**, Sorrento Therapeutics; **B. Cooley**, Sorrento Therapeutics; **M. Royal**, Sorrento Therapeutics;

V. Strand, AbbVie, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb(BMS), Boehringer-Ingelheim, Chemocentryx, Celltrion, Genentech/Roche, Gilead, GlaxoSmithKlein(GSK), Inmedix, Janssen, Kiniksa, Merck/MSD, Novartis, Pfizer, Regeneron Pharmaceuticals, Rheos, R-Pharma, Samsung, Sandoz, Sanofi, Scipher, Setpoint, Spherix, Aria, Bioventus, Blackrock, Equilibrium, Glenmark, Horizon, Kypha, Lilly, MiMedx, Sorrento, Tonix, Priovent; **J. Goldman**, Sorrento Therapeutics; **R. Querubin**, Sorrento Therapeutics; **R. Ross**, Sorrento Therapeutics.

To cite this abstract in AMA style:

Smith A, Roerig P, Cason J, Fancis D, Cooley B, Royal M, Strand V, Goldman J, Querubin R, Ross R. Lymphatic Delivery of Etanercept Achieves Significant Improvements in Rheumatoid Arthritis Disease Measures at 50% of the Standard Dose for Patients with an Inadequate Response to Subcutaneous Injections [abstract]. *Arthritis Rheumatol*. 2022; 74 (suppl 9).

<https://acrabstracts.org/abstract/lymphatic-delivery-of-etanercept-achieves-significant-improvements-in-rheumatoid-arthritis-disease-measures-at-50-of-the-standard-dose-for-patients-with-an-inadequate-response-to-subcutaneous-injectio/>. Accessed November 9, 2022.

ACR Meeting Abstracts - <https://acrabstracts.org/abstract/lymphatic-delivery-of-etanercept-achieves-significant-improvements-in-rheumatoid-arthritis-disease-measures-at-50-of-the-standard-dose-for-patients-with-an-inadequate-response-to-subcutaneous-injectio/>