

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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PURPOSE

We report interim results from a 10-patient Phase 1b clinical trial in moderate to severely active RA patients and a history of inadequate responses to etanercept. Patients were switched from 50 mg SC weekly dose to weekly lymphatic treatment with 25 mg etanercept administered using a novel nanotopography-microneedle (NTM) device that has been shown in rats to continuously deliver up to 40-fold higher lymphatic concentrations than IV, SC, or ID injections. **(Figure 1)**

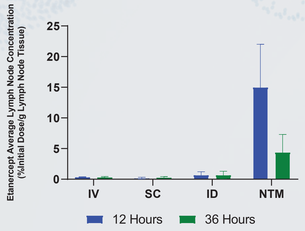


Figure 1: *Average etanercept concentration in axillary and inguinal lymph nodes in rats at 12 and 36 hours after dosing 1 mg over 1 hour.*

BACKGROUND

The lymphatic system is known to play an integral role in the pathology of rheumatoid arthritis[1] and mediates local RA flares[2], yet most biologic therapies are dosed SC or IV.

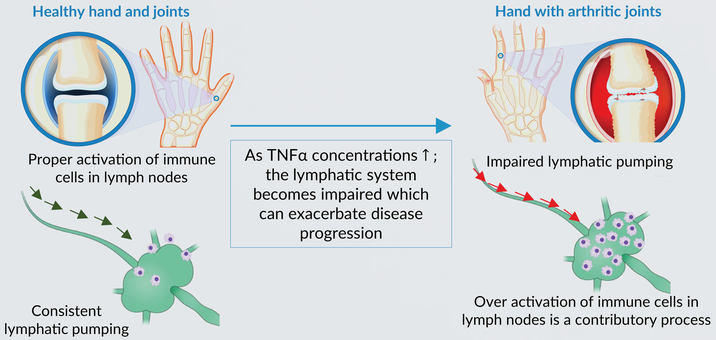


Figure 2: *Over-production of TNFα promotes swelling in the lymph nodes and decreased lymphatic pumping fuel joint swelling, pain, and overall disease progression[3, 4]. Re-directing TNF inhibitor therapy to the lymphatics and lymph nodes may restore lymphatic pumping and improve TNFα neutralization to achieve an improved clinical response at lower doses.*

METHODS

The NTM device was applied to the dorsal forearm and etanercept infused over 1.25 hours. The device was alternately applied between the left and right forearms every other week for 12 weeks. Lymphatic imaging was conducted using Near-Infrared Fluorescence with indocyanine green dye[5] to evaluate delivery into the lymphatic vessels and draining axillary lymph nodes, and to determine if lymphatic function (pump rates) improved after treatment.

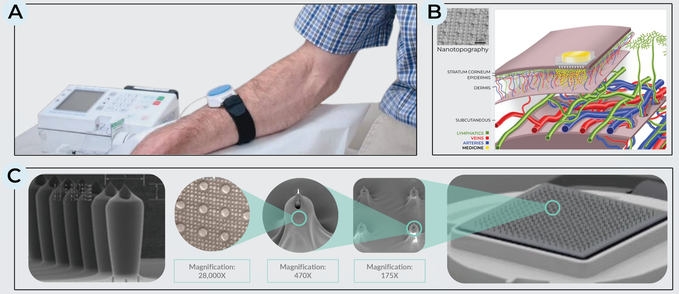


Figure 3: ***(A)*** *Image of NTM device on patient's dorsal forearm during lymphatic treatment,* ***(B)*** *Illustration of NTM device delivering through the epidermis skin layer and into the initial lymphatics, and* ***(C)*** *Image of NTM device microneedle array, nanotopography film on each microneedle, and microneedles.*

RESULTS

Lymphatic treatment significantly reduced disease activity (DAS28) inadequate responding patients without local adverse events or drug delivery-related immune responses **(Figure 4)**. Patient Global Assessment of Disease Activity and Patient Disease Pain concomitantly decreased **(Figure 5).**

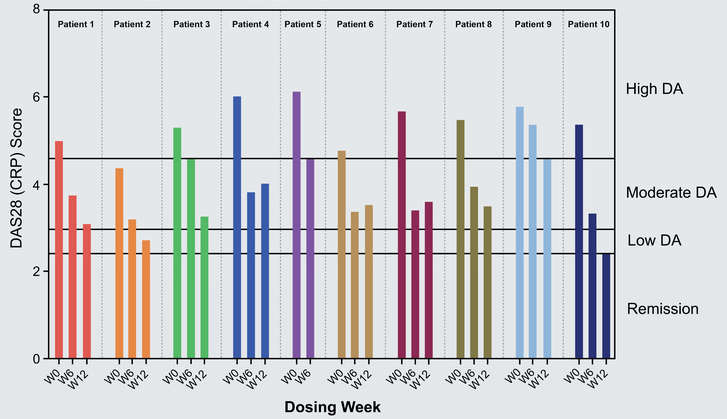


Figure 4: Disease scoring and metrics in patients treated using lymphatic delivery of etanercept. ***(A)*** *DAS28(CRP) levels at W0 (baseline), W6, and W12.*

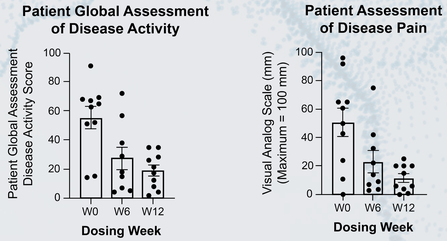


Figure 5: Disease Assessment of Activity and Pain in patients treated using lymphatic delivery of etanercept. *Left: Patient Global Assessment of Disease Activity, Right: Patient Assessment of Disease Pain. Data are represented as mean ± SEM (SEM is the standard error).*

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 6).**

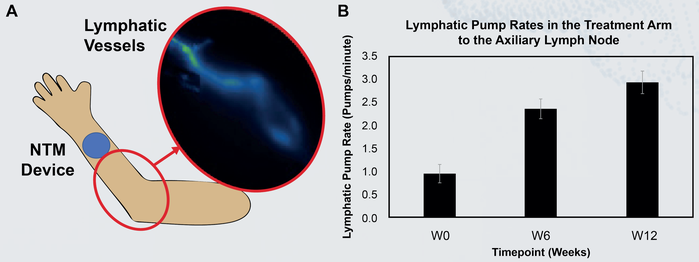


Figure 6: Improvements in lymphatic function from week 0 (W0) to 12 (W12) from lymphatic delivery of etanercept. ***(A)*** *Shows the NTM device dosing location on the patient and where the lymphatic vessels were imaged with indocyanine green dye. (B) Compares the lymphatic pump rates at W0 (baseline) to after 6 weeks (W6) and 12 weeks (W12) dosing. Data are presented as mean ± SEM.*

CONCLUSIONS

- **In RA patients with an inadequate response to etanercept 50 mg SC and moderate to severe RA by DAS scores, lymphatic delivery at half the dose was able to produce significantly improved DAS scores and lymphatic function.**
- **The lymphatic treatments were well tolerated with no SAEs and only mild erythema and pinpoint blood drops at the application site. One patient exhibited a rash once out of 22 treatments.**
- **These data underscore the importance of directing TNFα inhibitors locoregionally via the lymphatics and draining lymph nodes in the treatment of RA.**

REFERENCES

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