Tc99m Tilmanocept Imaging Can Differentiate the Fibroid Pathotype of Rheumatoid Arthritis from Non-Fibroid Pathotypes in Patients

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Introduction

The primary objective of this study is to assess the relationship between joint-specific Tc99m tilmanocept (TIL) uptake values and the pathobiology of RA-involved joint tissue. The cellular composition of RA-inflamed joints is known to vary between patients and is frequently separated into one of three pathotypes: fibroid, diffuse myeloid, and lympho-myeloid. Knowledge of an individual RA patient's pathotype may be clinically important because it may predict to which RA therapy a patient is likely to respond. Imaging with TIL (Fig. 1) offers the potential to distinguish between pathotypes without need of invasive biopsy. We hypothesized that the TIL imaging signal will correlate with the number and density of activated macrophages in the joints of RA patients, and that this imaging signal can provide important information about not only the disease status of the patient, but also indicate which pathotype of RA the patient has.

Tc 99m Tilmanocept

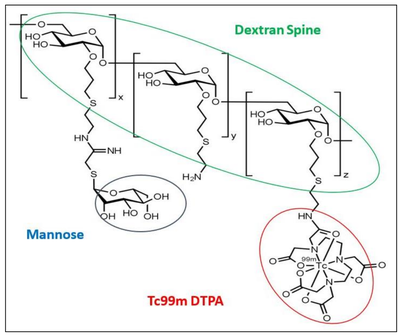

Figure 1. Tc 99m Tilmanocept is a synthetic molecule designed to bind with high affinity to macrophage mannose receptors (CD206). Frequently in RA, large numbers of CD206+ macrophages infiltrate into the synovial spaces of inflamed joints.

Methods

- Thirteen RA patients from a Phase 2b trial (NCT04078191) with active RA (DAS28 ≥ 3.2; ACR/EULAR 2010 Classification Criteria ≥ 6), at least one hand/wrist joint with a minimum ultrasound gray-scale synovitis score of 2 (range 0 to 3), and on stable therapy were enrolled.
- Hand/wrist planar gamma camera images were obtained one hour post IV administration of TIL.
- Quantitative image analysis was performed prior to biopsy. Images were quantitatively assessed to detect localization within synovial spaces of bilateral hands and wrists by determining average pixel intensity in each region of interest relative to average pixel intensity in an adjacent reference region, followed by comparison to a normative database of healthy control subject reference value ~~images~~.
- This quantification is performed for each patient and is termed the global Tilmanocept Uptake Value (TUV_{global}).
- Synovial immunohistochemistry (IHC) evaluations of single-joint biopsy specimens were used to quantify the degree of immunofluorescence of immune markers including: CD3, CD20, CD55, TE-7, CD68, CD163, and CD206.
- IHC evaluations were used to characterize the pathotype of the corresponding synovial specimens (as diffuse myeloid, lympho-myeloid, or fibroid) by an expert reader. The expert reader was blinded to the imaging results.
- TUV_{global} scores were compared to pathotype to determine if pathotypes could be distinguished quantitatively with TIL imaging.

Results & Discussion

- Image analysis conducted before the biopsies was able to separate the subjects into at least 2 distinct and nonoverlapping classes.
- TIL uptake in RA-inflamed joints was able to discretely differentiate patients with the fibroid pathotype (i.e., low macrophage involvement) from those having either the diffuse myeloid or lympho-myeloid pathotypes of RA (i.e., higher macrophage involvement) (Fig. 2 and 3).
- Eight of the subjects had relatively low levels of TIL uptake. All of these subjects were found to have the fibroid pathotype (one had limited tissue available but was called likely fibroid).
- Of the remaining 5 subjects, 4 had the diffuse myeloid pathotype and 1 had the lympho-myeloid pathotype.
- Those subjects with either the diffuse myeloid or lympho-myeloid pathotypes had, on average, 3.8x the TIL uptake as determined by TUV_{global} than the average subject with the fibroid pathotype.

Results & Discussion

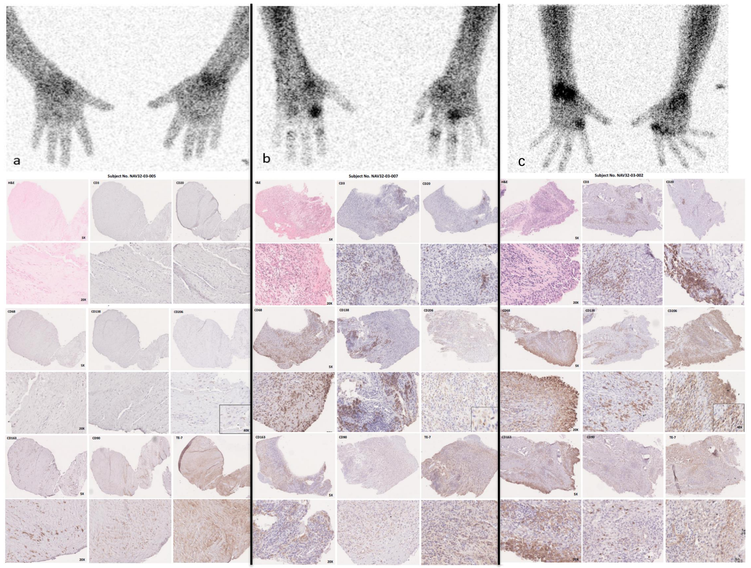

Figure 2. TIL imaging can distinguish between fibroid and non-fibroid pathotypes. Representative images of RA patients with the fibroid (a) diffuse myeloid (b) and (c) lympho-myeloid pathotypes.

IHC images (bottom panels) demonstrate differential patterns of immunological cell types characteristic of each of the pathotypes.

Results & Discussion

Subject	Global TUV	Pathotype
32-03-006	1.81	Fibroid
32-03-005	2.67	Fibroid
32-03-014	3.52	Fibroid
32-01-003	3.89	Fibroid
32-01-001	3.99	Fibroid
32-03-009	5.04	Fibroid
32-03-003	5.77	Fibroid
32-02-002	5.83	Likely fibroid
32-03-011	10.52	Diffuse Myeloid
32-03-007	11.51	Diffuse Myeloid
32-03-002	12.26	Lympho-myeloid
32-01-005	17.86	Diffuse Myeloid
32-01-002	25.74	Diffuse Myeloid
Average		
Fibroid	4.07	
Diffuse Myeloid	16.41	
Lympho-myeloid	12.26	

Figure 3. Image-derived TUV_{global} scores of each patient along with pathologically determined pathotype. Fibroid pathotype patients demonstrate low TIL uptake compared to diffuse myeloid and lympho-myeloid.

Conclusions

- These results support the hypothesis that TIL imaging can differentiate the fibroid pathotype of RA from non-fibroid pathotypes.
- The ability to reliably determine if a patient has the fibroid pathotype of RA from a single scan, a "virtual biopsy", could have significant implications for patient classification and therapy selection
- Further biopsy and imaging data will examine whether the diffuse myeloid vs. the lympho-myeloid pathotypes can also be discriminated.