Tc99m Tilmanocept Imaging Predicts Clinical Response in Rheumatoid Arthritis Patients Beginning New Anti-TNFα Therapy

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Introduction

- Effective and expeditious control of rheumatoid arthritis (RA) disease activity using a treat-to-target (T2T) strategy is crucial to prevent long term joint damage and disability.
- T2T often uses a trial-and-error approach in selecting therapeutics with clinical response assessments after 3-6 months.
- If patients do not reach a low disease activity state or remission, the cycle of trial and error is often repeated until satisfactory disease control is achieved, resulting in long delays before reaching low disease activity.
- Imaging with Tc99m tilmanocept (TIL; Figure 1) may provide an early predictor of clinical response, generating an objective, quantifiable readout of changes in macrophage density in joint inflammation of patients undergoing initiation or change of bDMARD therapy.
- Changes in macrophage density may be observed within weeks of treatment initiation, long before many clinical readouts used in standardized disease assessments become apparent.

Tc 99m Tilmanocept

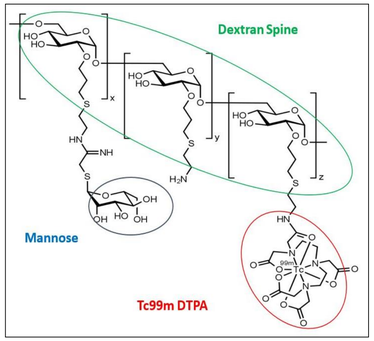

Figure 1. Tc 99m Tilmanocept is a synthetic molecule designed to bind with high affinity to macrophage mannose receptors (CD206). Frequently in RA, large numbers of CD206+ macrophages infiltrate into the synovial spaces of inflamed joints.

Methods

- 30 RA patients from a Phase 2b trial (NCT03938636) with active RA (DAS28 ≥ 3.2; ACR/EULAR 2010 Classification Criteria ≥ 6) set to start anti-TNFα therapy were enrolled and followed for 24 weeks.
- Hand/wrist planar gamma camera images were obtained one hour post IV administration of TIL at baseline prior to initiation of new treatment, as well as at 5, 12, & 24-weeks post-therapy initiation (N= 28/30 subjects; 2 lost to follow up).
- 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 images.
- A panel of established clinical assessments (ACR 20/50/70, CDAI, DAS28, HAQ-DI) was performed at each time point to compare imaging results with clinical evaluations.

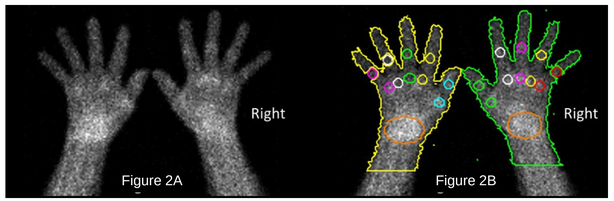

Figure 2. Planar images (anterior view) of the hands and wrists of a representative RA patient. Figure 2A shows the image without regions of interest (ROIs) that are used to calculate the joint and overall Tilmanocept Uptake Value (TUV_{joint} and TUV_{global}, respectively). Figure 2B shows the same image with placement of joint ROIs and whole hand reference regions. The reference regions are comprised of all the pixels enclosed by the yellow (left hand) and green (right hand) outlines of the hands, excluding the joint ROIs (small circles and ovals).

Results & Discussion

- In 27/30 subjects, TIL imaging from baseline to week 5 predicted ACR50 response at 12 weeks (Figure 3).
- For 24/28 subjects, TIL imaging from baseline to week 5 was predictive of ACR50 response at 24 weeks (Figure 3).
- There were 5 ACR50 responders at both weeks 12 and 24.
- Using ACR70 response as representation of clinical outcome, 25/30 subjects were correctly predicted at 12 weeks and 27/28 at 24 weeks (Figure 3).
- Truth tables were generated comparing ACR50 clinical response or non-response at weeks 12 and 24, demonstrating high specificity (0.96 at weeks 12 and 24), positive predictive value (PPV), and negative predictive value (NPV) (week 12: PPV=0.75, NPV=0.92; week 24: PPV=0.67, NPV=0.88).
- Sensitivity values (week 12= 0.6; week 24= 0.4) were possibly influenced by the low number of ACR50 responders in this cohort (N=5).
- Mean time from original diagnosis with RA of ACR50 responders and non-responders was 6.2 years and 9.1 years, respectively, at Week 24 (p=0.46).
- Combining TIL quantitative image analysis with the clinical markers ESR, RF, and HAQ-DI in a multivariate model gave an AUC of 0.97 for prediction of treatment response at week 24.
- Intravenous TIL was safely tolerated in all subjects.

Figure 3. Number of cases TIL imaging predicted correctly and incorrectly at Weeks 12 and 24 at the ACR50 and ACR70 response levels.

ACR50/ACR70 Response (30 Subjects Wk12; 28 Wk24)				
	ACR50		ACR70	
	Week 12	Week 24	Week 12	Week 24
Total Predicted Correctly	27	24	25	27
Total Predicted Incorrectly	3	4	5	1

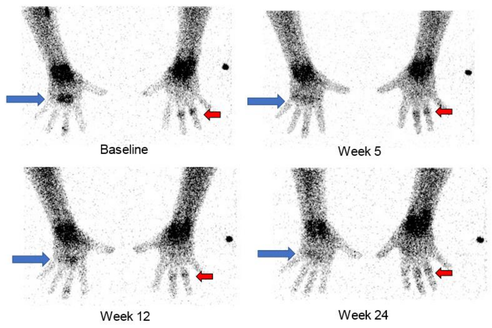

Figure 4. Longitudinal TIL images of the hands and wrists of RA patient 09-013, who achieved ACR50 response at Weeks 12 and 24 (and ACR70 at Week 24), showing reduction of localization in joints over time. TUV_{global} also reflected this longitudinal diminution of localization, and correctly predicted the ACR50 response at both Weeks 12 and 24 and the ACR70 response at Week 24. The small, circular marker represents the right side. Image gray-scale is inverted for display purposes.

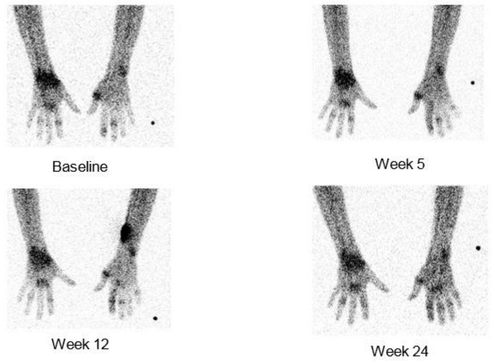

Figure 5. Longitudinal TIL images of the hands and wrists of RA patient 07-004, who achieved only an ACR20 response at Week 12, and no response (ACR20 or greater) at Week 24. Note that localization remains relatively constant over time, with some joints even exhibiting an increase in localization. This was reflected in the image quantification. Note that the Week 12 image displays extravasation of Tc99m tilmanocept in the right forearm.

Conclusion

- Results indicate that marked changes in TIL global uptake values by week 5 presage clinical efficacy evaluations at week 12 and week 24 of treatment and demonstrate that tilmanocept imaging can provide quantifiable imaging assessment of RA-involved joints that enables an objective, early prediction of clinical response.
- Tc99m tilmanocept is currently in Phase 3 (clinicaltrials.gov identifier: NCT05246280) for indications centered on early prediction of treatment response to anti-TNFα therapy.