EVALUATION OF INTRAVENOUS INJECTION OF ^{99M}TC-TILMANOCEPT IN STATIC PLANAR GAMMA EMISSION IMAGING AND FUSED SPECT/CT IMAGING FOR RHEUMATOID ARTHRITIS

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Abstract

Background/Purpose: Activated macrophages play a critical role in RA by perpetuating inflammation via TNFα release and participating in the destruction of bone and cartilage. Notably, macrophages are the dominant cell type in the synovial sublining of RA-affected joints. Thus, specific detection of activated macrophage infiltration in RA patients may provide valuable immunodiagnostic insight towards joint inflammation, destruction and overall disease progression. Tc 99m Tilmanocept is a synthetic radiopharmaceutical imaging agent that binds to the activated macrophage mannose receptor (CD206) with high affinity. It is currently under investigation for intravenous (IV) administration in subjects with RA in a dose escalation study. The purpose of this report is to communicate safety and imaging findings from RA subjects who received the maximum study dose of 400 µg tilmanocept/10 mCi Tc 99m.

Methods: Nine subjects with clinically diagnosed RA were enrolled in the trial. All subjects received IV administration of 400 µg of tilmanocept radiolabeled with either 10 mCi (n=3), 5mCi (n=3), or 1 mCi (n=3) Tc 99m. Static planar gamma emission images of the whole body and affected joints were acquired at 60 and 180 min post injection with additional SPECT/CT imaging of affected joints.

Results: No adverse events were observed after IV administration of 400 µg Tc 99m tilmanocept radiolabeled with 1, 5, or 10 mCi of Tc 99m. There was strong correlation of radiotracer localization to affected joints observed in gamma emission imaging. SPECT/CT imaging further demonstrated that Tc 99m tilmanocept localization is specific to the PIP, MCP, knees, ankle, shoulder, elbow, and periarticular synovial spaces and not in cortical bone or osseous marrow spaces.

Conclusion: Overt joint-specific localization of Tc 99m tilmanocept activity was visualized in affected joints of all subjects who had undergone multiple RA flares despite previous successful treatments, which demonstrates macrophage infiltration of these joints as a key component of disease. IV injection of Tc 99m tilmanocept at the maximum study dose was well-tolerated with no adverse events. These findings, in addition to prior biopsy evaluations from other subjects, confirm activated CD206 macrophage infiltration to be a key component of RA pathology which can be safely and effectively visualized on gamma emission imaging with Tc 99m tilmanocept.

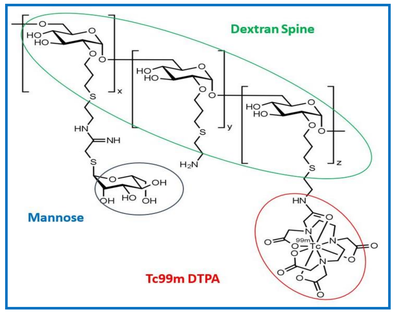
Introduction

Rheumatoid arthritis (RA) is a common, chronic, systemic, progressive, autoimmune disease causing inflammation and pathology throughout the body, but perhaps most noticeably in the peripheral joints of the skeleton. In the affected joints, RA is characterized by macrophage and lymphocyte infiltration, proliferation of synovial fibroblastic tissue, and joint destruction. Worldwide, about one adult in every 200 has RA. If not successfully treated, joint inflammation and destruction in RA patients can lead to crippling loss of function, severe chronic pain, and disfigurement of joints. Therefore, there is a significant and growing need to manage RA patients more effectively to limit the morbidity and mortality caused by RA.

Recently, antirheumatic drugs (DMARDs) have dramatically improved outcomes for many RA patients. Three problems persist: 1] DMARDs are most effective when RA symptoms first appear, which is problematic for current RA diagnostics; 2] monitoring the effectiveness of DMARD therapy is challenging; and 3] a significant portion of RA patients respond poorly or not at all to current DMARDs. This indicates that early and accurate diagnosis of RA affords a “window of opportunity” for the greatest probability of effective RA therapy and the possibility of disease remission.

Activated macrophages play a critical role in RA by perpetuating inflammation via TNFα release. and participating in the destruction of bone and cartilage. Notably, macrophages are the dominant cell type in the synovial sublining of RA-affected joints. As a result, synovial macrophage numbers correlate with radiographically determined joint destruction in RA. In humans, macrophage infiltrations of synovial tissues are present when RA patients first develop clinical symptoms. Therefore, detection of the density or numbers of macrophages in inflamed joints may facilitate more sensitive and specific identification of RA patients as soon as they present with symptoms and early in the course of their illness when DMARDs are likely to be most effective.

^{99m}Tc-Tilmanocept



99mTc-Tilmanocept is a wholly synthetic molecule designed specifically to bind with high precision, specificity, and accuracy to macrophage mannose receptors (CD206). In RA, large numbers of CD206 expressing macrophages infiltrate into the synovial spaces of inflamed joints. It is currently under investigation for intravenous (IV) administration in subjects with RA in a dose escalation study.

Methods

The primary objective of this study was to determine the safety and tolerability of escalating doses of Tc 99m tilmanocept. The secondary objective was to determine the localization of Tc 99m tilmanocept by SPECT (single photon emission computed tomography) imaging in subjects with active RA and asymptomatic controls and concordance of localization with clinical symptomology.

Table 1: Nine subjects with clinically diagnosed RA received IV administration at the maximum study dose (400 µg) of Tc 99m tilmanocept. These subjects received the Tc 99m tilmanocept with one of 3 radiolabel doses:

1 mCi, 5 mCi, or 10 mCi.

Table 1	Tilmanocept Mass Dose
Specific Radioactivity	400 µg
10 mCi	Group 3 (n = 3 RA)
5 mCi	Group 6 (n = 3 RA)
1 mCi	Group 9 (n = 3 RA)

At 60 minute and 180 minute post injection, static planar gamma emission images of the subject’s whole body were acquired. Planar images with both hands were also taken at these time points. Additionally, SPECT/CT images were taken of identified joints of interest.

The primary endpoint was to find the proportion of subjects not experiencing pharmacologic activity or an adverse drug reaction in each group. The secondary endpoints were to determine the per subject and per joint localization rate of Tc 99m tilmanocept by SPECT or SPECT/CT imaging.

Results & Discussion

No adverse events were observed after IV administration of 400 µg Tc 99m tilmanocept radiolabeled with 1, 5, or 10 mCi of Tc 99m. High-level 99mTc-tilmanocept uptake was readily visible and detectable across RA affected joints. There was strong correlation of radiotracer localization to affected joints observed in gamma emission imaging. SPECT/CT imaging further demonstrated that Tc 99m tilmanocept localization is specific to the PIP, MCP, knees, ankle, shoulder, elbow, and periarticular synovial spaces and not in cortical bone or osseous marrow spaces. The data suggest that the level of inflammation is strongly related to macrophage infiltration and ultimately image signal (**See Figures 1 and 2**).

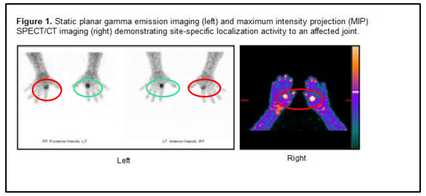


Figure 1. Static planar gamma emission imaging (left) and maximum intensity projection (MIP) SPECT/CT imaging (right) demonstrating site-specific localization activity to an affected joint.

Figures 1 and 2 showing the localization (●●●●) and binding of 99mTc tilmanocept to macrophage mannose receptors of RA inflamed joints.

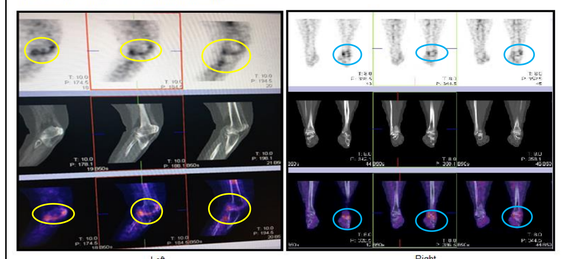


Figure 2. Fused SPECT/CT images of RA subjects defining the localization of Tc 99m tilmanocept to the periarticular synovial space of the knee (left) and ankle (right).

Conclusion

Overt joint-specific localization of Tc 99m tilmanocept activity was visualized in affected joints of all subjects who had undergone RA flares despite previous successful treatments. This demonstrates macrophage infiltration of these joints is a key component of disease progression. IV injection of Tc 99m tilmanocept at the 400 µg dose was well-tolerated with no adverse events. These findings, in addition to prior biopsy evaluations from other subjects, confirm activated CD206 macrophage infiltration to be a key component of RA pathology which can be safely & effectively visualized on γ-emission imaging with Tc 99m tilmanocept and may be valuable in evaluating patient response to joint inflammation therapies.