

Overview of ^{99m}Tc -anti-TNF- α scintigraphy: diagnostic applications

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Abstract: Tumor necrosis factor alpha (TNF- α) has a role in the pathogenesis of several inflammatory diseases such as rheumatoid arthritis, Crohn's disease, and ulcerative colitis. As TNF- α plays a role in the pathogenesis of different inflammatory diseases, anti-TNF- α agents (monoclonal antibodies [mAbs]) such as infliximab, adalimumab, and certolizumab have been developed and investigated for the treatment of these conditions. In recent years, these mAbs also have been used for diagnosis, monitoring, follow-up of disease activity, and therapy decision-making for inflammatory diseases, especially rheumatoid arthritis, after labeling with ^{99m}Tc . However, ^{99m}Tc -anti-TNF- α imaging might have severe adverse effects and is expensive. In contrast, scintigraphic imaging before therapy with radiolabeled mAbs may be a cost-effective solution for therapy decisions.

Keywords: monoclonal antibodies, mAb, nuclear medicine, ^{99m}Tc tumor necrosis factor- α imaging

Introduction

Monoclonal antibody (mAb) targets are adhesion molecules, activation markers, antigens, or receptors. mAbs interact with some inflammation pathways at the molecular level. For diagnostic processes, mAbs can be labeled with radionuclides, using direct or indirect methods.

Anti-tumor necrosis factor alpha (TNF- α) antibodies such as infliximab, adalimumab, and certolizumab are used in the treatment of TNF- α -mediated inflammatory diseases.¹ Infliximab, produced by a recombinant cell culture technique, has been approved by the US Food and Drug Administration for the treatment of moderate-to-severe active rheumatoid arthritis. Soluble and membrane-bound TNF- α are the targets of infliximab, which specifically binds to TNF- α .² This complex inhibits the binding of TNF- α to its receptor, as well as inhibiting the biological activity of TNF- α .³ Infliximab does not have an effect on TNF- β (lymphotoxin α). The median terminal half-life of infliximab is 9.5 days.

TNF- α plays different roles: it induces some cytokines and acute-phase reactants; activates eosinophils and neutrophils; and enhances the endothelial layer permeability.⁴

Discussion

A study was performed by Conti et al in which they performed scintigraphy in a patient with arthritis to evaluate TNF- α -mediated inflammation degree in an affected knee.⁵ The researchers imaged the patient scintigraphically with infliximab before and 4 months

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after intraarticular therapy. Planar images of the inflamed joint were acquired at 6 and 24 hours after injection of ^{99m}Tc -infiximab. The researchers observed dense accumulation in the affected knee, and they determined that this accumulation was related to a high level of intralesional TNF- α . In the studies performed 4 months after intraarticular infiximab therapy, the authors evaluated the knee with disease and found no uptake in the inflamed joint. In addition, examination of the patients' clinical features using clinical parameters, including erythrocyte sedimentation rate, C-reactive protein level, and visual analog scale, showed that complete remission was reached. Therefore, the researchers concluded that TNF- α scintigraphy could be a good guide in the evaluation and follow-up of intraarticular treatment.⁵

Another study was performed by Chianelli et al in rheumatoid arthritis, using scintigraphy with ^{99m}Tc -infiximab.⁶ Imaging with ^{99m}Tc -infiximab was performed before and 3 months after intraarticular infiximab therapy. In the follow-up imaging, radiopharmaceutical uptake of several amounts was seen in the affected joints. The authors concluded that inflamed joints demonstrated distinctive uptake compared with normal joints. They also emphasized that uptake in inflamed joints showed a correlation with clinical recovery and swelling reduction. They suggested that TNF- α scintigraphy might be important not only for evaluation of symptomatic joints but also for examining asymptomatic joint involvement.

D'Alessandria et al used ^{99m}Tc -infiximab scintigraphy in patients with Crohn's disease.⁷ Their aim was to demonstrate the presence of TNF- α within the gut mucosa in patients with active Crohn's disease. Ten patients with active Crohn's disease refractory to conventional medical therapies were imaged 6 to 20 hours after intravenous injection of 10 mCi ^{99m}Tc -infiximab. One week after this imaging, the researchers performed a survey of ^{99m}Tc -hexamethylpropyleneamine-oxime-labeled autologous white blood cells. The authors found that ^{99m}Tc -infiximab uptake of the inflamed bowel was less than that of ^{99m}Tc -hexamethylpropyleneamine-oxime-labeled autologous white blood cells. However, when anti-TNF- α therapy was tried, there was a response to therapy in two of the patients, despite no uptake being seen in ^{99m}Tc -infiximab imaging. Thus, the authors concluded that the mechanism of anti-TNF- α therapy is related to peripheral blocking of TNF- α , rather than TNF- α downregulation in the bowel.⁷

Another ^{99m}Tc -anti-TNF- α mAb used in diagnosis and treatment is adalimumab. This antibody was approved by the US Food and Drug Administration in December 2002 as

a therapeutic approach to rheumatoid arthritis and psoriatic arthritis. Labeling of adalimumab with ^{99m}Tc was done via indirect radiolabeling.⁸ Soluble and membrane-bound TNF- α are recognized by adalimumab.⁹ Adalimumab has fewer adverse effects than other antibodies.¹⁰

Barrera et al¹¹ performed a study in patients with active rheumatoid arthritis. Their aim was to consider the susceptibility and biodistribution of radiolabeled adalimumab.¹¹ They completed two scintigraphic imaging scans for each patient: one before treatment with ^{99m}Tc -adalimumab and another after treatment with nonradiolabeled anti-TNF- α mAb or an intramuscular injection of corticosteroid. The authors observed that same-time injection of nonradiolabeled TNF- α mAb reduced ^{99m}Tc -TNF- α mAb uptake by the joint. This retention demonstrated that the radiolabeled mAb target in arthritic joints is the TNF- α . In the group which received corticosteroids, the disease condition was reduced, which led to a decrease in uptake of the radiopharmaceutical. The authors concluded that ^{99m}Tc -adalimumab could be used to find clinical changes in disease progress and that this radiopharmaceutical is an advantage for specific evaluation of the inflamed joints.¹¹

Malviya et al¹² performed a study in patients with rheumatoid arthritis. Their aim was to conclude which radiopharmaceutical should be used for treatment and follow-up.¹² They processed scintigraphic imaging with ^{99m}Tc -infiximab and ^{99m}Tc -adalimumab, respectively, in 12 and nine patients with active rheumatoid arthritis. Two imaging scans were done: one before and the second 3 months after local therapy with infiximab or systemic therapy with adalimumab. The authors found no differences in biodistribution between two radiopharmaceuticals. In addition, in two of the patients, the researchers performed ^{99m}Tc -human immunoglobulin (HIG) scintigraphy. In these two patients, the authors observed that although clinical response was seen, there was no decrease in the ^{99m}Tc -HIG uptake of the joints after the cold anti-TNF- α mAb treatment. In conclusion, the authors emphasized that for the evaluation of therapy, response in patients with active rheumatoid arthritis for unlabeled mAb ^{99m}Tc -TNF- α antibodies was superior to that for ^{99m}Tc -HIG scintigraphy.

In another study, performed in 2012 by Malviya et al, the researchers examined 20 patients with chronic inflammatory autoimmune disease. They imaged all patients with ^{99m}Tc rituximab before treatment with nonradioactive rituximab. The imaging was performed 6 and 20 hours after radiopharmaceutical treatment. The authors concluded that imaging with specifically labeled agents might be an advantage for cost-effectiveness and therapy evaluation in patients treated with biological agents.¹³

Table 1 Summary of research performed with ^{99m}Tc-Anti-TNF- α scintigraphy

Study	Radiopharmaceutical	Experimental/ clinical	Number of cases	Disease	Results
Conti et al ⁵	^{99m} Tc infliximab	Clinical	Case reports	Spondylarthropathy	It is a guide for evaluation and prognosis
Chianelli et al ⁶	^{99m} Tc infliximab	Clinical	7 patients	Rheumatoid arthritis	It is important for more detailed diagnosis
D'Alessandria et al ⁷	^{99m} Tc infliximab	Experimental/ clinical	9 mice, 10 patients	Crohn's disease	Tumor necrosis factor- α mechanism of action should be known for therapy decision
Barrera et al ¹¹	^{99m} Tc adalimumab	Clinical	10 patients	Rheumatoid arthritis	It is specific for treatment and inflamed joints evaluation
Malviya et al ¹²	^{99m} Tc infliximab and ^{99m} Tc adalimumab	Clinical	19 patients	Rheumatoid arthritis	Therapy evaluation with tumor necrosis factor- α is better than other scintigraphic imaging
Lopes et al ¹⁴	^{99m} Tc-anti-tumor necrosis factor- α monoclonal antibody	Clinical	Case report	Graves ophthalmopathy	New target-based modalities for diagnosis and therapy
Malviya et al ¹³	^{99m} Tc infliximab	Clinical	20 patients	Chronic inflammatory autoimmune diseases	For cost effectiveness, scintigraphic imaging is needed

Finally, in a case published by Lopes et al,¹⁴ the authors emphasize that ^{99m}Tc-anti-TNF- α mAb could also be used in the diagnosis of Graves ophthalmopathy. For the diagnosis of Graves ophthalmopathy, different imaging methods can be used. However, ^{99m}Tc-anti-TNF- α scintigraphy could be a promising method for the diagnosis of active ocular disease. The researchers showed unilateral Graves ophthalmopathy by imaging with ^{99m}Tc-anti-TNF- α mAb because TNF- α is thought to be enrolled in the initial active phase of disease development.¹⁴ Thus, imaging with ^{99m}Tc-anti-TNF- α mAb might be the first step of new target-based modalities for the diagnosis and therapy of Graves ophthalmopathy (Table 1).¹⁴

Conclusion

All our research with mAbs guide us to the conclusion that more research should be carried out on the cost-effectiveness of ^{99m}Tc-anti-TNF- α mAb imaging.

Disclosure

The authors report no conflicts of interest in this work.

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