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Currently Available Radiopharmaceuticals for Imaging Infection and the Holy Grail

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Abstract

Infection is ubiquitous. However, its management is challenging for both the patients and the healthcare providers. Scintigraphic imaging of infection dates back nearly half a century. The advances in our understanding of the pathophysiology of disease at cellular and molecular levels have paved the way to the development of a large number of radiopharmaceuticals for scintigraphic imaging of infection. These include radiolabeling of blood elements such as serum proteins, white blood cells (WBCs), and cytokines, to name a few. Infectious foci have also been imaged using a radiolabeled sugar molecule by taking advantage of increased metabolic activity in the infectious lesions. Literature over the years has well documented that none of the radiopharmaceuticals and associated procedures that facilitate imaging infection are flawless and acceptable without a compromise. As a result, only a few compounds such as ^{99m}Tc-hexamethylpropyleneamineoxime, ¹⁸F-FDG, the oldest but still considered as a gold standard ¹¹¹In-oxine, and, yes, even ⁶⁷Ga-citrate in some countries, have remained in routine clinical practice. Nonetheless, the interest of scientists and physicians to improve the approaches to imaging and to the management of infection is noteworthy. These approaches have paved the way for the development of numerous, innovative radiopharmaceuticals to label autologous WBCs ex vivo or even those that could be injected directly to image infection or inflammation without direct involvement of WBCs. In this review, we briefly describe these agents with their pros and cons and place them together for future reference.

Introduction

Infection is a major problem for patients who experience it and clinicians who manage the disease. Accurate and early diagnosis can be difficult and time-consuming, whereas delays in diagnosis can be life-threatening. Therefore, accurate detection and localization of infection and inflammation at an early stage is of vital importance for patient management, as well as for the cost containment. History, physical examination, various laboratory tests such as erythrocyte sedimentation rate, and C-reactive protein measurement are performed

to determine onset of infection. For localization of infection, however, radiologic methods such as X-ray, ultrasonography, computed tomography, magnetic resonance imaging, and nuclear medicine imaging methods are used. These methods, however, suffer from limitations and cannot reliably detect infection at an early stage.

Most radiopharmaceuticals required for nuclear medicine imaging are designed to accumulate in infection by increased capillary blood flow and increased vascular permeability, or are associated with migration of leukocytes. In general, therefore, nuclear medicine imaging of infection is derived from the pathophysiologic course of infection, and can detect infection and inflammation in an early phase before the appearance of morphologic changes at the site of infection.¹⁻⁶

The quest for scintigraphic imaging of infection dates back to early 1970s, following the serendipitous observation of accumulation of ⁶⁷Gallium (⁶⁷Ga) citrate, 4 days following its administration for imaging Hodgkin disease.⁷ However, 1976 marked a new chapter in the history of imaging infection; McAfee and Thakur surveyed nearly 100 radioactive compounds for labeling autologous white blood cells (WBCs) ex vivo.^{8,9} The survey led to the development of ¹¹¹Indium (¹¹¹In)-oxine as the most efficient lipid-soluble agent, to label WBCs ex vivo and to image experimental abscesses in an animal model¹⁰ and pyogenic abscesses in man.¹¹ Although now more than 4 decades have elapsed, ¹¹¹In-oxine is still considered as gold standard for WBC labeling in routine practice for imaging infection. Nonetheless, the technique of labeling WBCs ex vivo suffers from numerous limitations and falls short of the ideal requirements outlined in the Table.^{4,5} To address these issues over the years, a score of novel radioactive compounds with innovative hypotheses have been evaluated.¹⁻⁴

This review briefly describes these agents, including their strengths and limitations,

Radiopharmaceuticals

⁶⁷Ga-Citrate

⁶⁷Ga-citrate was one of the first radiopharmaceuticals used for scintigraphic imaging of infection.⁷ ⁶⁷Ga-citrate, after intravenous (i.v.) administration, binds primarily to transferrin and to other iron binding proteins such as lactoferrin, ferritin, and bacterial siderophores. A large percentage is excreted via the kidneys in the first 24 hours after injection and relatively small proportion in bowel in the first week. Radioactivity therefore is seen in the kidneys, bladder, abdominal region, and in organs rich in lactoferrin such as the eyes and lactating breasts. Physiologic activity is also seen in the bone, bone marrow, liver, spleen, and soft tissues. Forty-eight hours after its administration, variable physiologic activity is also seen in the lacrimal glands, salivary glands, and breast tissue (Fig). In children, uptake in the thymus is also observed.

⁶⁷Ga-citrate is sensitive for imaging acute infection, chronic infection, and inflammation. ⁶⁷Ga-citrate imaging is also useful in fever of unknown origin (FUO), vertebral osteomyelitis, and opportunistic infections in immunocompromised patients. However, its specificity is compromised because of uptake in many normal tissues as well as in tumors. A

major drawback of ^{67}Ga -citrate, however, is its slow blood clearance, which compels imaging to be performed at 48 and sometimes up to 72–96 hours after administration.^{2,4,6,12}

Ex Vivo Labeling of Leukocytes

^{111}In -Oxine

With the hypothesis that the above lack of specificity of ^{67}Ga -citrate could be eliminated with the use of autologous WBCs, which spontaneously migrate to foci of infection physiologically, McAfee and Thakur initiated their survey of agents to radiolabel WBC for imaging infection.^{8,9} Subsequently, conclusion that ^{111}In -oxine was the agent of choice to label WBC for imaging infection was drawn.^{10,11}

For such labeling, venous blood is drawn from the patient into a sterile, disposable plastic syringe. Red cells are sedimented, and the carefully separated leukocyte-rich plasma is centrifuged to obtain WBCs. After these cells are labeled with ^{111}In , they are reinfused back into the patient intravenously.¹

Thakur et al¹¹ also demonstrated that ^{111}In -oxine, a lipid-soluble agent, passively diffuses through the cell membrane and binds to cytoplasmic components of the cells, provides a stable label, and serves to follow the cell trafficking in vivo. ^{111}In -labeled leukocytes once injected intravenously accumulate in the lungs in a large proportion and then clear from the lungs in approximately 4 hours. ^{111}In -labeled leukocytes also accumulate in the spleen, liver, and bone marrow. Accumulation of radioactivity in the spleen and liver is also supplemented by red cells, lymphocytes, and platelets that may be present in the separated autologous leukocytes and labeled with ^{111}In . Although patient imaging can be performed 4–6 hours post injection of labeled leukocytes, best results are achieved at imaging 24 hours later.^{1,11,12}

Radiolabeled WBCs are used to image FUO, osteomyelitis, infected orthopedic hardware, inflammatory bowel disease (IBD), abdominal infection, pelvic sepsis, and other inflammatory processes. Sensitivity of this method is ~90% for acute and chronic infection. In vitro WBC labeling involves multiple steps and is time-consuming. In addition, there is a possible risk associated with ex vivo handling of blood that may be tainted with hepatitis B, hepatitis C, or HIV.^{1,2}

Other ^{111}In Agents

^{111}In -oxine binds to transferrin in plasma and requires plasma to be removed during cell labeling. This may compromise cell viability. To address this issue, lipophilic agents such as ^{111}In -acetylacetone (ACAC) and tropolone were developed.^{11,13,14}

In contrast to ^{111}In -oxine, ^{111}In -ACAC and ^{111}In -tropolone have been shown to label WBC in a plasma medium. ^{111}In -tropolone-labeled WBC clear from the lungs in a shorter period of time than those WBC labeled with ^{111}In -oxine in saline. In addition, ^{111}In -tropolone-labeled WBC migrate to the inflammation quickly, therefore infections can be detected in less than 4 hours after injection. However, some investigators observed that ^{111}In -tropolone-labeled WBC had compromised chemotactic characteristics. Other authors found ^{111}In -

ACAC and ^{111}In -tropolone were less appealing than ^{111}In -oxine to label WBC for imaging infection.^{13,15}

In 1985, simple kit formulation of ^{111}In -2-mercaptopyridine-N-oxide (Merc), a nontoxic, water-soluble agent was evaluated to label human platelets efficiently. This new agent was also evaluated for labeling canine leukocytes in plasma.¹³ MERC binds ^{111}In as avidly as tropolone, provides labeling in a plasma medium, and does not affect cell viability. ^{111}In -Merc-labeled leukocytes are cleared from the lungs quickly and accumulate in the abscesses rapidly.^{13–15} The preparation process for labeling WBC with ^{111}In -Merc was also less cumbersome than ^{111}In -oxine. However, ^{111}In -Merc did not become a widely used agent for WBC labeling.^{2,7,15}

$^{99\text{m}}\text{Tc}$ HMPAO

$^{99\text{m}}\text{Tc}$ -hexamethylpropyleneamineoxime (HMPAO) is a second-generation radiopharmaceutical to label leukocytes introduced by Peters et al in 1986.^{16,17} $^{99\text{m}}\text{Tc}$ -HMPAO is a lipophilic agent that labels WBC predominantly. HMPAO is available commercially as a lyophilized powder (kit) ready to be labeled when needed with generator-produced $^{99\text{m}}\text{Tc}$. Alternatively, $^{99\text{m}}\text{Tc}$ -HMPAO can be bought commercially as a single-use dose. The half-life of $^{99\text{m}}\text{Tc}$ ($t_{1/2}$: 6 hours) is long enough to allow imaging to be carried out without excessive radioactivity decay having occurred, but not too long to induce unnecessary radiation burden long after imaging has been performed. In addition to the lower radiation dose of $^{99\text{m}}\text{Tc}$ than ^{111}In , the decay characteristics of $^{99\text{m}}\text{Tc}$ (140 Kev) are more favorable to image using a gamma camera. Image quality with $^{99\text{m}}\text{Tc}$ is therefore better than with ^{111}In . Because of the low radiation dose with $^{99\text{m}}\text{Tc}$ -WBC, imaging can be repeated if required.^{18,19} $^{99\text{m}}\text{Tc}$ elutes out of the WBCs labeled with $^{99\text{m}}\text{Tc}$ -HMPAO. This, in part, leads to a very different distribution of $^{99\text{m}}\text{Tc}$ -HMPAO-WBC than ^{111}In -oxine-labeled WBC. With $^{99\text{m}}\text{Tc}$ -HMPAO-labeled WBC, radioactivity is seen in urine, bladder, gall bladder, bone marrow, and gastrointestinal system, especially in the colon. Nearly 6% of $^{99\text{m}}\text{Tc}$ is excreted in the stool in 48 hours.^{1,2,16} Also, nonspecific activity is seen in the kidneys. Such a distribution of radioactivity contributes to false-positive results. $^{99\text{m}}\text{Tc}$ -WBC is therefore less useful for imaging abdominal infection. For imaging renal, genitourinary, and gastrointestinal infection, therefore, ^{111}In -WBC is preferred.^{1,12,20}

^{18}F -FDG

Over the past few years, ^{18}F -FDG has been increasingly used for imaging infection. The use of ^{18}F -FDG is driven by its 2 important virtues. First, ^{18}F is a cyclotron-produced positron emitting radionuclide that facilitates PET imaging and the other is that ^{18}F -FDG is taken up by WBC through glucose transporter, GLUT-1, and then is phosphorylated, allowing ^{18}F to monitor WBC distribution in vivo. For imaging infection, ^{18}F -FDG is used in 2 ways: (1) by labeling WBC ex vivo and (2) by injecting it directly in vivo.^{21–23}

Ex Vivo ^{18}F -FDG-Labeled WBC

Rini et al²⁴ in 2006, labeled WBC ex vivo and PET-imaged infection in vivo. This investigation provided promising results. However, the short half-life of ^{18}F ($t_{1/2}$ -110 minutes) is practically too short for the relatively lengthy ex vivo WBC labeling procedure,

and prevents delayed imaging when needed. Furthermore, in various studies, it was reported that the WBC labeling efficiency (LE) with ^{18}F -FDG was much lower and more variable than with ^{111}In oxine. Although not examined in detail, the leukocyte glucose transporter expression, the serum glucose levels, and the presence of intrinsic proteins have been thought to affect the LE. Additionally, excessive wash-out of ^{18}F from ^{18}F -FDG-labeled WBC was also discouraging. These prevented the use of ^{18}F -FDG-WBC from routine clinical practice from imaging infection.^{25,26}

Directly Injected ^{18}F -FDG

Directly injected ^{18}F -FDG has therefore remained a much preferable approach to image infection. Not only is the approach convenient but it also provides high sensitivity for imaging infection. The limitations, however, are the lack of specificity rendered by excessive ^{18}F -FDG uptake by the metabolic activity of many normal organs such as the heart, brain, and muscle, as well as in the kidneys and bladder caused by urinary excretion. ^{18}F -FDG for imaging infection requires the patient to fast before injection and in the case of diabetic patients, blood glucose levels to be monitored before the administration of ^{18}F -FDG.^{27–30}

^{18}F -FDG-PET/CT is used for evaluation of patients with FUO with high sensitivity (90%) and specificity (97%). ^{18}F -FDG PET/CT has a high negative predictive value for determining etiologies of FUO (negative predictive value 100%). Furthermore, ^{18}F -FDG-PET/CT imaging has high diagnostic value for the evaluation of children with FUO and unexplained origin of inflammation.^{31–33}

Other PET Imaging Compounds

^{64}Cu -Tropolone

Copper-64 (^{64}Cu) is an emerging positron emitting radionuclide used extensively primarily in preclinical and translational oncologic PET imaging. Chelated with tropolone ^{64}Cu was investigated to label WBC.²⁵ Poor intra-WBC retention of ^{64}Cu prompted Bhargava and colleagues^{26,34} to add to the WBC incubation mixture a membrane-permeable fluorinated divalent chelator MF/AM (2-(2-amino-4-methyl-5-fluorophenoxy) methyl-8-aminoquinoline-N, N, N', N'-tetra-acetic acid), which improved labeling yield as well as the ^{64}Cu -intra-WBC retention. Post-labeled cell viability was not compromised. Although no further studies could be found, the longer half-life of ^{64}Cu may be a better substitute for PET imaging of infection than ^{18}F -FDG-WBC.

^{89}Zr Compounds

^{89}Zr compounds for labeling WBCs have been also investigated. In 1 investigation, ^{89}Zr - or ^{64}Cu -labeled chitosan (CN) nanoparticles were used to label WBC presumably by phagocytosis. Mixed WBCs were separated from human blood. ^{89}Zr -CN-labeled WBCs had higher LE than ^{64}Cu -CN-labeled WBCs.³⁵ ^{89}Zr -CN-labeled WBCs showed less elution of radioactivity than ^{64}Cu -CN-labeled WBC. Although the 78.4-hour half-life of ^{89}Zr could be considered too long for PET imaging of infection, the ^{89}Zr tracer shall be highly useful to follow the in vivo kinetics of such cells as T cells or platelets.

To follow in vivo cell trafficking, Sato et al developed a ^{89}Zr -oxine complex for labeling dendritic cells, cytotoxic T cells, and natural killer cells.³⁶ Labeling did not compromise the viability of dendritic cells and cytotoxic T cells, and function of T cells. The lipid solubility of ^{89}Zr -oxine made it useful to label.

Another compound of ^{89}Zr namely ^{89}Zr -oxalate was also investigated to image inflammation and tumors. Although exact mechanism of inflammatory cell binding was not determined, tumor imaging results showed that ^{89}Zr -oxalate had higher uptake in macrophages than other cells in the tumor. The authors also reported that ^{89}Zr -oxalate had higher tumor specificity than ^{18}F -FDG. Data suggest that exploring the use of ^{89}Zr -oxalate to label WBCs ex vivo or even in vivo may be worthwhile.³⁷

In Vivo Labeling of WBC

The advent of receptor-specific monoclonal antibodies (mAb) combined with the better understanding of the receptor expression on human WBC led to the field of labeling human WBC in vivo using radiolabeled mAbs. The major thrust of these investigations was driven by the objectives of eliminating the disadvantages associated with the procedures required to label WBC ex vivo. Although several mAbs were evaluated, 4 were examined in humans. Three of them targeted various epitopes of nonspecific cross-reacting antigen (NCA), namely NCA-47, NCA-90, and NCA-97. The fourth one targeted stage-specific embryonic antigen-1 (SSEA-1). All of them were of murine origin and were not humanized. The pros and cons of them are briefly described below.

NCA-47 Antibody

The anti NCA-47 was the first murine mAb (IgG₁) that was labeled with ^{123}I iodine (^{123}I) ($t_{1/2}$: 13.3 hours), 159 KeV (83%), and investigated to image infection in humans. All inflammatory or infectious lesions were successfully imaged without adverse events.^{38,39}

Anti NCA-90

This anti NCA-90 antibody presented 2 advantages over the anti NCA-47 antibody stated above. First, the antibody (IMMU-MN3) was fragmented (Fab'), which facilitated faster clearance; and second it was labeled with a generator-produced and commonly used radionuclide $^{99\text{m}}\text{Tc}$ ($t_{1/2}$: 6.1 hours, γ -140 KeV: 90%). Also known as LeukoScan, the mAb is commercially available in Europe and has been used extensively in humans. After i.v. administration, approximately 4% of administered $^{99\text{m}}\text{Tc}$ was bound to circulating neutrophils. In vivo elution of $^{99\text{m}}\text{Tc}$ was reported. Despite the limitations, the convenience makes its use attractive. It is used in humans to image osteomyelitis, prosthetic joint infections, soft tissue infections, and pulmonary aspergillosis. False-positive results in patients were reported.^{40,41}

Anti NCA-95 ($^{99\text{m}}\text{Tc}$ -BW250/183)

A murine monoclonal IgG₁ antibody, BW250/183 (Behring-Werke, Marburg), also binds to NCA-95 receptors on the neutrophils.⁴² It was labeled with $^{99\text{m}}\text{Tc}$. At least 10% of this agent was bound to granulocytes in blood at 45 minutes after i.v. administration. An

important and serious side effect of ^{99m}Tc -labeled BW250/183 (besilesomab, Santimum[®]) is dose-dependent human anti-mouse antibody formation. Uptake of ^{99m}Tc -BW250/183 was very high in the spleen and bone marrow, whereas the uptake in infection foci was low. Moreover, higher dose of ^{99m}Tc -BW250/183 caused neutropenia that took several hours for recovery.^{43,44}

^{99m}Tc -Anti-SSEA-1 (Anti Cluster Differentiation-15)

Anti-SSEA-1 is an IgM class of mAb and it is produced by immunizing mice with murine embryonal carcinoma F9 cells. SSEA-1 antigen cluster differentiation-15 is expressed on human granulocytes.⁴⁵ Thakur and colleagues labeled murine IgM monoclonal anti-SSEA-1 (MCA-480) with ^{99m}Tc , also called ^{99m}Tc -fanolesomab, LeuTech, or NeutroSpec. It binds to CD15 glycoproteins with high affinity (10^{-11}). CD15 is expressed on the human granulocyte membranes in high density. The authors found that anti-SSEA-1 was the most desirable agent for specific labeling human neutrophil in vivo, as approximately 50% of the injected ^{99m}Tc was bound to circulating polymorphonuclear leukocytes (PMNs) quickly after i.v. injection.^{45–48}

It was shown that ^{99m}Tc -fanolesomab played an important role in imaging equivocal appendicitis. Sensitivity, specificity, and accuracy were found to be 91%, 86%, 87%, respectively. The sensitivity, specificity, and accuracy for imaging osteomyelitis were 90%, 67%, 76%, respectively.⁴⁹ This agent was investigated on patients with clinical evidence of acute inflammatory processes at the time of imaging. All these patients had accurate positive images.⁴⁶ ^{99m}Tc -fanolesomab also imaged prosthetic vascular graft infection safely and accurately (95%). No adverse reactions were reported in patients by any user.⁵⁰ It was approved by the US Food and Drug Administration for suspected appendicitis in 2004. Later, however, it caused serious adverse reactions in 2 patients, which resulted in its withdrawal from market in late 2005.^{51–53}

Other Monoclonal Antibodies

Radiolabeled Anti-Tumor Necrosis Factor-Alpha Monoclonal Antibody

Tumor necrosis factor-alpha (TNF α) is a proinflammatory cytokine that plays an important role in inflammation.⁵⁴ Anti-TNF antibodies such as infliximab, adalimumab, golimumab, certolizumab pegol, and etanercept have been developed to treat inflammatory diseases such as rheumatoid arthritis (RA), spondyloarthropathy, psoriatic arthritis, and IBDs.^{55–61}

Among them, infliximab was labeled with ^{99m}Tc and evaluated to image persistent knee arthritis. Scintigraphy showed high uptake in the affected knee, which had a high level of TNF before the treatment. Four months after treatment, there was no uptake in the affected knee, so scintigraphy verified the efficiency of the treatment.⁶²

^{99m}Tc -infliximab scintigraphy was also used in patients with active and refractory monoarthritis. Target-to-background ratios were higher in patients with affected joints than nonaffected joints before treatment. The authors concluded that ^{99m}Tc -anti-TNF mAb scintigraphy can play an important role for choosing the best treatment option for each patient and can minimize the number of unnecessary anti-TNF treatments.⁶³

Adalimumab labeled with ^{99m}Tc using succinimidyl-hydrazinonicotinamide (S-HYNIC) was used for imaging patients with RA.⁶⁴ In this study, inflamed joints were distinctly visualized, but the uptake was not prominent in smaller inflamed joints, probably because of the absence of TNF in those joints.⁶⁵

Malviya et al evaluated both ^{99m}Tc -labeled infliximab and adalimumab for scintigraphic imaging of RA in patients, before and 3 months after intra-articular treatment with infliximab or systemic therapy with adalimumab. After the treatment, ^{99m}Tc -anti-TNF mAb scintigraphic images showed decreased uptake in the affected joints, which correlated with the improved clinical symptoms.⁶⁶

Radiolabeled Anti-CD4 Monoclonal Antibody

CD4 antigen is located on T-cells and macrophages. CD4 plays an important role in RA. CD4-specific scintigraphy was therefore thought to be a useful method for imaging patients with RA, to improve diagnosis and treatment of the disease. ^{99m}Tc -labeled anti-human CD4 mAb (MAX. 16H5) showed increased uptake in the RA lesions.^{67,68}

Steinhoff et al⁶⁹ performed ^{99m}Tc -anti-CD4-Fab (^{99m}Tc -EP1645) scintigraphy for evaluation of inflammatory activity in patients with RA. They also assessed the safety and tolerability of ^{99m}Tc -anti-CD4-Fab (^{99m}Tc -EP1645) in patients with active synovitis secondary to RA and determined the potential of ^{99m}Tc -anti-CD4-Fab (^{99m}Tc -EP1645) as a marker to assess the disease activity in a phase I study. The results demonstrated that ^{99m}Tc -anti-CD4-Fab (^{99m}Tc -EP1645) scintigraphy was a promising approach to evaluate CD4-specific inflammatory activity and to determine the effectiveness of RA therapy.

Radiolabeled Anti-CD20 Monoclonal Antibody

CD20 is expressed on the surface of both normal and malign T lymphocytes. Rituximab is a chimeric murine or human mAb against the CD20 antigen, and has been used for treatment of active RA resistant to TNF.

Rituximab labeled with ^{99m}Tc was used in patients to image various inflammatory and autoimmune diseases including RA. Significant uptake was observed in the inflamed joints, and it was correlated with clinical findings of patients. No adverse events were noted.^{70,71}

Radiolabeled Anti-CD3 Monoclonal Antibody

CD3 is expressed on the T lymphocytes. The murine mAb, muromonab, namely OKT-3, is specific for the CD3 receptor. Muromonab is an immunosuppressant used to prevent acute rejection in transplant patients.

^{99m}Tc -labeled anti-CD3 mAb, muromonab (OKT-3) was used in patients with RA to show inflamed synovium.⁷² ^{99m}Tc -OKT-3 uptake was seen in painful joints. ^{99m}Tc -anti-CD3 mAb imaging can be preferred for assessing the treatment effectiveness in patients with RA. However, utilization of it was abandoned because of the side effects.^{73,74}

A humanized anti-CD3 mAb, visilizumab (Nuvion), was also labeled with ^{99m}Tc and used in animals. But no further work in human was noted.⁷⁵

Anti-E-Selectin Monoclonal Antibody

selectin, a 115 kDa glycoprotein, and endothelial-specific adhesion molecule, is expressed on the luminal surface of the vascular endothelium. The expression of vascular endothelial E-selectin, which plays an important role in the inflammation, is stimulated by proinflammatory cytokines, and promotes adhesion of neutrophils, monocytes, and eosinophils to activated vascular endothelium through carbohydrate ligands such as sialyl Lewis X. The increased expression of E-selectin occurs in various inflammatory diseases, such as RA and IBD. ^{111}In -labeled anti-E-selectin mAb imaging was successfully performed initially in an animal model and then also in humans.^{76–79}

Bhatti et al showed that ^{111}In -labeled anti-E-selectin mAb imaging can localize affected parts of bowel, the extent of Crohn's disease, and ulcerative colitis. ^{111}In -labeled anti-E-selectin mAb imaging was reported to be superior to $^{99\text{m}}\text{Tc}$ leukocyte imaging.⁷⁶

Jamar et al^{77,78} compared $^{99\text{m}}\text{Tc}$ -human immunoglobulin (HIG) and a ^{111}In -anti-E-selectin mAb (1.2B6) in patients with RA and synovitis. The investigators noted that ^{111}In -labeled anti-E-selectin mAb was more sensitive, and specific than $^{99\text{m}}\text{Tc}$ -HIG scintigraphy. $^{99\text{m}}\text{Tc}$ -labeled anti-E-selectin (1.2B6) Fab fragment was more specific than $^{99\text{m}}\text{Tc}$ -hydroxydiphosphonate bone scintigraphy shows synovitis in another study.^{78,79}

Human Polyclonal Immunoglobulin-G

HIG labeled with $^{99\text{m}}\text{Tc}$ or ^{111}In has also been used to image infection or inflammation. Three possible mechanisms of accumulation, namely, capillary leak, binding Fc part of IgG to Fc receptors on granulocytes, and binding of IgG to bacteria are postulated. Radiolabeled HIG has been shown to be suitable for FUO in particular immunodeficient patients. The disadvantage, however, is its high blood pool activity that compromises its usefulness in routine clinical practice.^{80,81} $^{99\text{m}}\text{Tc}$ -HIG is able to show actively inflamed joints, even in patients with serum-negative RA, in a greater extent than other anatomical imaging methods. Sensitivity and specificity of $^{99\text{m}}\text{Tc}$ -HIG are reported to be 83.3% and 92%, respectively.⁸²

Radiolabeled Antibiotics

In an attempt to differentiate bacterial infection and sterile inflammation, antibiotics that penetrate bacterial cell wall and kill microorganisms by various mechanisms were radiolabeled and evaluated.^{83,84}

The most commonly used among them to image infection is $^{99\text{m}}\text{Tc}$ -ciprofloxacin (Infecton).⁸⁵ Ciprofloxacin is a synthetic broad-spectrum fluoroquinolone antibiotic that binds to bacterial DNA gyrase and inhibits DNA synthesis.^{86,87} $^{99\text{m}}\text{Tc}$ -ciprofloxacin is primarily excreted from the kidneys and has low liver and bowel uptake.⁸⁸ Ciprofloxacin was also labeled with ^{68}Ga and ^{18}F .^{89,90} ^{68}Ga -ciprofloxacin was shown to be a good bacteria-specific imaging agent in an *Staphylococcus aureus* (*S. aureus*) infected rat model. ^{18}F -ciprofloxacin, however, was not a successful imaging agent.^{89–91}

Clinical studies of $^{99\text{m}}\text{Tc}$ -Infecton have concluded that Infecton is a good bacterial infection imaging agent for the assessment of tuberculosis, FUO, osteomyelitis, orthopedic prosthesis,

spinal infection, abdominal infections, and infection in immunosuppressed patients.^{92–95} Less promising results, however, have been reported by other investigators.^{96,97}

Other promising antibiotics have been ^{99m}Tc-cefazolin, ^{99m}Tc-cefepime, ^{99m}Tc-clarithromycin, ^{99m}Tc-rufloxacin, ^{99m}Tc-ceftriaxone, ^{99m}Tc-levofloxacin, ^{99m}Tc-gemifloxacin, and ^{99m}Tc-sitafloxacin, with target-to-nontarget ratio higher than 8.⁸⁴

Additionally, radiolabeled antibiotics such as ^{99m}Tc-rifampicin, ^{99m}Tc-nitrofurantoin, ^{99m}Tc-amoxicillin, ^{99m}Tc-alafosfalin, 2-deoxy-2-[¹⁸F]fluoroacetamido-D-glucopyranose, ^{99m}Tc-vancomycin, ^{99m}Tc-kanamycin, ^{99m}Tc-erythromycin, ^{99m}Tc-azithromycin, ^{99m}Tc-clarithromycin, ^{99m}Tc-clindamycin, ^{99m}Tc-mebendazole, and ^{99m}Tc-2,2'-(8-hydroxyquinolin-7-yl) methylazanediy] diacetic acid complex have also evaluated.^{98–110}

Fungal Imaging

Radiolabeled Fluconazole

Among the triazole antifungal agents, fluconazole is the most commonly used compound for the treatment of *Candida* infections in severely immunocompromised patients. Fluconazole inhibits ergosterol synthesis with binding to cytochrome P450. ^{99m}Tc-labeled fluconazole is a promising imaging agent for imaging *Candida albicans* infections. ^{99m}Tc-fluconazole is quickly excreted via the kidneys and has low liver uptake. However, ^{99m}Tc-fluconazole accumulated poorly in bacterial infections and in *Aspergillus fumigatus* infections in mice. Fluconazole was also labeled with ¹⁸F for PET imaging. ¹⁸F-labeled fluconazole is more lipophilic than ^{99m}Tc-labeled fluconazole, so it showed higher accumulation in liver than ^{99m}Tc-labeled fluconazole. Uptake of ¹⁸F-fluconazole in infection foci was also low.^{111,112}

Radiolabeled Chitinase

Chitin is found in fungal cell and renders chitin a promising candidate to image fungal infection.^{113,114} ¹²³I-labeled chitinase B was investigated in fungal infection in mice. Results were encouraging.¹¹⁴ Chitin binding protein (CBP21) was also labeled with ^{99m}Tc via a chelating agent HYNIC. Uptake of this agent in fungal infections was higher than in bacterial infections. The authors concluded that it is a new promising agent to distinguish fungal from bacterial infection.¹¹³

Nanoparticles

Two types of nanoparticles namely human serum albumin nanocolloids and lipid liposomes, a few nanometer in size, were labeled with either ^{99m}Tc or ¹¹¹In, and injected directly to image infection in experimental animals and in humans.^{115–122} The sensitivity of imaging infection (87%) in 1 study was as good as or better than ¹¹¹In-labeled leukocyte scintigraphy (81%).¹²² Regional “spilling” of the tracer into the extravascular space through increased capillary permeability was proposed as the probable mechanism of uptake.¹²³ The widespread use of these nanoparticles in routine clinical practice was compromised probably because of the adverse reactions the use of particles presented.¹²⁴

Vitamins

Biotin

Biotin (vitamin H) binds to avidin, a protein commonly available in the eggs of avians, amphibians, and reptiles. ^{111}In -biotin nonspecifically accumulates at the inflammation site by increased capillary permeability. Approximately 4 hours after ^{111}In -biotin is injected, avidin is administered via i.v. The ^{111}In -biotin-avidin complex is formed, which quickly clears through the kidneys with minimal uptake by normal tissue. A high target-to-background ratio for early imaging is thus achieved. ^{111}In -labeled biotin scintigraphy has been shown to be an important imaging method for spinal infections in patients.^{125–129} SPECT/CT increased the efficacy of ^{111}In -biotin scintigraphy in the management of patients with spine infections.¹³⁰

Vitamin B12

Vitamin B12 (cyanocobalamin) (Cbl) is a significant enzyme cofactor necessary for rapid replication of cells and bacteria.¹³¹ Vitamin B12 was labeled with either $^{99\text{m}}\text{Tc}$ or ^{111}In via bifunctional chelating agents, and was evaluated to distinguish bacterial infection from sterile inflammation. Initial results were highly encouraging.¹³²

Chemotactic Peptides

Chemotactic compounds are attractants that are secreted by microorganisms to which are attracted white blood cells. This movement of an organism in response to a chemical stimulus is known as chemotaxis. In the case of pyogenic infection, PMNs are attracted to the various chemotactic stimuli released by the invading microorganism. One of the well-characterized stimuli is a peptide N-formyl-met-leu-phe (FMLP). With the hypothesis that radiolabeled FMLP, once administered intravenously, shall bind to circulating PMNs for convenient imaging of infection, Zoghbi et al¹³³ labeled FMLP with ^{111}In . Resultant neutropenia in a rabbit model prevented further investigations.

Ten years later, Fishman et al prepared FMLP analogs, labeled them with $^{99\text{m}}\text{Tc}$. Further investigations in animals witnessed persistent neutropenia.^{134–137}

Chemokines and Cytokines

Chemokines are signaling proteins secreted by cells. Their name is derived from their ability to induce directed chemotaxis in nearby responsive cells. Cytokine proteins are classified as chemokines according to their behavior and structural characteristics. Lymphocytic T cells and macrophages are main sources of cytokines. Cytokines are responsible for homeostatic control of the immune system. Cytokines interact with specific cell membrane receptors, which exist primarily on leukocytes. Their expression of cytokine receptors are increased in the course of infection and inflammation. Radiolabeled cytokines with low molecular weight, short circulating time, high affinity for binding to the specific receptors, and human recombinant origin to prevent immunogenicity can in principle label WBCs in vivo.^{135,138–140}

Tuftsins consist of an Fc portion of IgG. Tuftsin receptor is expressed on surface of neutrophils, monocytes, and macrophages, and it stimulates phagocytosis and chemotaxis by these cells.¹⁴¹ ^{99m}Tc-RP128, a tuftsin receptor antagonist, demonstrated promising results for imaging inflammation in patients with Crohn's disease and RA. No adverse events were reported.^{142–144}

Interleukin-1 (IL-1) is a proinflammatory cytokine that binds to receptors expressed on granulocytes, monocytes, and lymphocytes. ¹²³I-labeled IL-1 localized infectious foci in mice. In humans, however, serious adverse events prevented its further use.^{145–147}

IL-2 is expressed on activated T lymphocytes. It binds to IL-2 receptors with high affinity, which are expressed by activated lymphocytes during inflammation. It is responsible for sustaining the inflammatory reaction with stimulation of long-term proliferation of activated T lymphocytes, and proliferation and differentiation of natural killer cells, B cell lymphocytes, and macrophages. ^{99m}Tc- or ¹²³I-labeled IL-2 successfully showed T lymphocyte infiltration in various autoimmune and inflammatory diseases such as Hashimoto thyroiditis, Graves' disease, Crohn's disease, and celiac disease.^{148–153} ^{99m}Tc-labeled IL-2 showed the presence of insulinitis in patients with autoimmune diabetes.¹⁵⁴ In the meantime, labeling IL-2 with ¹⁸F was advocated.³

IL-6 binds to specific receptors expressed on neutrophils. ¹²⁵I-labeled IL-6 was used to image infection in mice. Accumulation of ¹²⁵I-IL-6 was lower than ¹²⁵I-IL-1.¹⁵⁵

IL-8 is a chemotactic cytokine that binds to CXC chemokine receptors on plasma membranes of neutrophils with high affinity. It plays an important role in infection and inflammation. It activates PMNs and provides their migration to inflammation or infection foci.^{156,157} ¹²⁵I-labeled recombinant human IL-8 (rhIL-8) localized acute inflammatory lesions in an animal model.¹⁵⁸ ¹³¹I-labeled rhIL-8 rapidly accumulated in lesions of osteomyelitis and cellulitis in patients.¹⁵⁹ IL-8 labeled with ^{99m}Tc, using HYNIC as a chelator, was also evaluated to image infection in an animal model. It quickly visualized infection but produced transient neutropenia.¹⁶⁰ ^{99m}Tc-IL-8 scintigraphy was performed in patients with suspected, localized infections. No significant side effects were seen.¹⁶¹ However, no further data are found in the literature.

IL-12 stimulates the differentiation of T lymphocytes and plays a role in the chronic inflammation. IL-12 receptor is expressed on peripheral mononuclear cells and is present on activated T lymphocytes and natural killer cells.^{162,163} ^{99m}Tc-HYNIC-IL-12 successfully imaged chemically induced chronic colitis in mice.¹⁶⁴

Platelet factor 4 binds to CXC type II (IL-8 type B) receptors, which are expressed on PMNs and monocytes. P483H peptide, which includes the heparin-binding region of platelet factor 4, was labeled with ^{99m}Tc and used to image *Escherichia coli* (E. coli) infections in rabbits and infection in patients. No adverse events were reported.^{165,166}

Leukotriene B₄ (LTB₄) is a chemotactic factor and expressed at a high level by granulocytes.¹⁶⁷ It was reported that radiolabeled LTB₄ antagonist against LTB₄ receptors can be used as an agent to image inflammation and infection. The results of this agent were

compared with various agents like ^{99m}Tc -HMPAO-labeled WBC. It was reported that DPC-11870 can clearly image abscesses. However, high-level distribution of this agent in bone marrow prevented its further use.^{168–170}

Antimicrobial Peptides

Equally important to imaging bacterial infection is determining the effectiveness of antibiotic treatment so that any over treatment could be prevented. In this quest, targeting proliferating microorganism can play an important role. Attempts have been made to target bacteria using radiolabeled antimicrobial peptides, which are the protein molecules of the innate immune system to protect the body from infection.¹⁷¹ Antimicrobial peptides with their amphipathic structure pass through the membrane and enter inside the target bacterial cell.¹⁷² Interaction with the bacterial plasma membrane by electrostatic and hydrophobic interaction composes the main part of their antimicrobial activity. Therefore, radiolabeled antimicrobial peptides can in principle differentiate bacterial infection from sterile inflammation and can determine effectiveness of antibiotic treatment.¹⁷³

Various radiolabeled antimicrobial peptides such as human neutrophil peptide, human lactoferrin, human ubiquicidin peptide fragment (UBI), and bacteriophages have been investigated for imaging of infection.^{174–178}

^{99m}Tc -labeled human neutrophil peptide-1 rapidly imaged bacterial infections in mice.¹⁷⁹ With a large protein such as ^{99m}Tc -labeled human lactoferrin, the imaging results, however, were not so preferable.^{173,180}

Various domains of UBI such as UBI 29–41, UBI 18–35, and UBI 31–38 were labeled with ^{99m}Tc and investigated for imaging bacterial infections.^{173,176} ^{99m}Tc -labeled UBI 29–41 differentiated bacterial and fungal infection from sterile inflammation in experimental animals and in humans.^{181–183} In a recent study, UBI fragments 29–41 and 31–38 were conjugated with NODAGA and labeled with ^{68}Ga and investigated for imaging infection. Specific uptake of the ^{68}Ga -NODAGA-UBI conjugates was observed in *S. aureus* in mice by PET imaging.¹⁸⁴

Bacteriophages 185 P22, E79, VD-13, and 60 were labeled with ^{99m}Tc and evaluated in vitro and in an infection mouse model.¹⁸⁶ Specific host binding was seen in vitro for all of the ^{99m}Tc -phages. Further investigations are warranted.

Annexin-V

Annexin is a common name for a group of cellular proteins. In humans, the annexins are found inside the cell. During bacterial invasion, PMNs are activated, migrate to the site of invasion, and phagocytose the microorganism. During the process, PMNs become apoptotic and externalize phosphatidylserine on their surface. Annexin-V, the endogenous protein, binds to phosphatidylserine with high affinity. With the hypothesis that radiolabeled Annexin-V selectively binds to apoptotic PMNs, Annexin-V was labeled with ^{99m}Tc and was successfully evaluated to image experimental abscesses in animals and infection in humans.^{187–190}

Like Annexin-V near infrared fluorophore ophore, named PSVue794, also binds to phosphatidylserine with high affinity. Five microgram of PSVue794 was administered intravenously to mice bearing bacterial infection and sterile infland mice were imaged optically at various predetermined times after injection. At 3 hours post injection, abscesses were clearly visualized (abscess/background 6.6 ± 0.2) with greater uptake than in the inflammation (inflammation/ background 3.2 ± 0.5).¹⁹¹ The progressive and promising development in optical imaging technology, may in the future, make this non-nuclear technology feasible to image infection in humans.^{191,192}

¹²⁴I-FIAU Fialuridine

Fialuridine, 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodouracil (FIAU) is a thymidine nucleoside analog. Bacterial thymidine kinase (TK) uses FIAU as a substrate. The mechanism of uptake of FIAU is similar to uptake of FDG in that FIAU is phosphorylated and trapped inside of bacteria by TK.^{193–196} However, not all bacteria have TK enzyme, which might limit its applications.¹⁹⁶

Nonetheless, Bettgowda et al developed a technique to label FIAU with ¹²⁵I and demonstrated focal infection in a mouse model. The investigators concluded that this agent can be used for focal bacterial infections in humans.¹⁹⁴

Diaz et al labeled FIAU with positron emitting ¹²⁴I for PET musculoskeletal bacterial infection in a group of 8 patients.¹⁹⁵ Encouraging results of this work prompted Zhang et al to image prosthetic joint infection in 6 patients. Results were similar to those of ¹¹¹In-WBC. The image quality, however, was inferior to that with ¹¹¹In-WBC. Although qualifies for PET imaging, the 5.4 d $t_{1/2}$ of ¹²⁴I may be considered too long for a diagnostic application of the radionuclide.¹⁹⁶

^{99m}Tc-Pheophorbide-A

Pheophorbide-α (PH-A) is a plant derivative photosensitizing agent, extracted from spirulina maxima algae. PH-A has been shown to have microbial activity both for gram (+) and gram (–) bacteria.

^{99m}Tc-labeled PH-A was investigated to image *S. aureus* infection in rats with ^{99m}Tc-PH-A. Target-to-nontarget radioactivity ratio was significantly higher than that of ^{99m}Tc-labeled antibiotics. The authors concluded that ^{99m}Tc-PH-A can be developed as a radiopharmaceutical to discriminate bacterial infection from inflammation.¹⁹⁷

¹⁸F-Labeled Maltohexaose

¹⁸F-labeled maltohexaose (¹⁸F-MH) is a novel PET imaging agent that targets bacteria-specific maltodextrin transporter not found in mammalian cells. This makes ¹⁸F-MH specific for viable bacteria and allows quick clearance from noninfected tissues. This, in turn, renders ¹⁸F-MH an agent with higher sensitivity and specificity than ¹⁸FDG to image pyogenic infection. As a commonly used food additive, ¹⁸F-MH has minimal toxicity in humans.

Consistent with this hypothesis, Ning et al showed ^{18}F -MH can image early-stage infections consisting of as few as 10^5 colony forming unit *E. coli* in rats. It may be possible that ^{18}F -MH can determine drug resistance and allow physicians to monitor the course of antibiotic treatment. Further work is warranted.¹⁹⁸

(1→3)- β -D-Glucan Aptamers

Glucans are found in cell membrane of some bacteria. Aptamers similar to antibodies have high affinity and specificity for glucans. Unlike antibodies, however, they are minimally immunogenic, and relatively inexpensive to synthesize and modify. Their small size allows them to penetrate into cells. Many radiolabeled aptamers have been used to image inflammation and infection in preclinical studies.^{199–201}

Santos et al evaluated $^{99\text{m}}\text{Tc}$ -labeled anti-*S. aureus* aptamers to detect bacterial infection. The $^{99\text{m}}\text{Tc}$ -radiolabeled aptamers were able to differentiate aseptic inflammation from bacterial infection.²⁰²

In another study, $^{99\text{m}}\text{Tc}$ -labeled (1→3)- β -D-glucan aptamers were evaluated to identify foci of fungal infection. The authors concluded that the use of aptamers for scintigraphic imaging of bacterial infections should be further investigated.²⁰³

Siderophores

Siderophores are iron transporters used by most living cells, including bacteria, and serve as a chelating agent for such metal ions as gallium or indium.

Siderophores such as triacetylfusarinine, ferrioxamine E, desferrichrome A, and desferrioxamine have been labeled with ^{68}Ga and ^{89}Zr , and compared for imaging *Aspergillus* infection.²⁰⁴ All of radiolabeled siderophores showed promising properties as radiopharmaceuticals for PET imaging of infection.²⁰⁵

Summary and Future Directions

Infection is ubiquitous yet heterogeneous. Formation of abscesses is a highly coordinated and a complex set of biological, biochemical, and pathologic events that protect a body from pathogenic invasion. One avenue that helps the physician in the management of this disease is the scintigraphic localization of occult abscesses. Investigations into approaches for imaging infection begun nearly half a century ago. However, the quest for finding an ideal agent to image infection continues until today.

The investigations to image infection began with a search for a radioactive agent that will label WBC effectively, yet preserve their viability, so that the labeled WBCs shall transport the radioactivity to the site of infection and allow it to be localized by external scintigraphic imaging. Although this approach has been highly successful in principle, it is far from ideal, primarily because of the processes that are required to label WBCs *ex vivo*. These weaknesses combined with the increased understanding of pathologic response to invading microorganism, at a cellular and a molecular level, have paved the way to the scholarly

approaches for the preparation and evaluation of numerous radioactive agents to image infection. Many of these are listed in this review with their pros and cons together with a few, such as ^{99m}Tc -HMPAO-labeled autologous WBC, ^{111}In -oxine-labeled autologous WBC, ^{18}F -FDG, and ^{67}Ga -citrate that are used in routine practice worldwide. Do they address all questions that need to be addressed for the management of patients with infection? No. Are they ideal for the routine clinical use? No. The questions then cross the mind of all those basic scientists and physicians who are closely involved with the field are (1) Will a single ideal agent ever be discovered that shall image all heterogeneous types of infections conveniently and reliably? (2) Will one require to use multiple agents that may be most suitable to localize a given type of infection and be able to distinguish it from inflammation or (3) Will the imaging examination performed using 1 agent shall permit physicians to prevent overtreatment of a patient? Looking closely at the half century old history of the development of the field, it is reasonable to conclude that the choice of the use of a particular radiopharmaceutical shall be governed by the convenience of its use and by the ability of a given radiopharmaceutical to address a specific question that may be needed to address for better management of the disease. We hope that this presentation providing a description of multiple radiopharmaceuticals with the underlying principals of their use and pros and cons of their applications shall be helpful in the future, in making such a choice.

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Figure.

Biodistribution in man of 14 most commonly used radiopharmaceuticals injected intravenously. ^{67}Ga -citrate and Fluorine-18-FDG are injected directly and ^{111}In (oxine) and $^{99\text{m}}\text{Tc}$ (HMPAO) WBC are injected after they are labeled ex vivo. Although different organ distribution of ^{67}Ga -citrate and ^{18}F -FDG should be expected, the distribution of ^{111}In -WBC and $^{99\text{m}}\text{Tc}$ -WBC should be similar. However it is not. Rapid in vivo, release of $^{99\text{m}}\text{Tc}$ from labeled WBC and its subsequent distribution different from those of the WBC, contribute to the difference and may lead to false-positive or false-negative images.

Table**Ideal Characteristics of a Radiopharmaceutical for Infection or Inflammation Imaging^{4,5}**

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- Specific to infection
 - Selective accumulation in infection foci
 - No uptake in noninflamed sites
 - No side effects, no toxicity, no immunogenic response
 - Fast clearance from normal tissues
 - Low cost
 - Easy preparation
 - The ability to distinguish infection from inflammation
 - Applicable for use in immunocompromised patients
 - Low marrow and renal accumulation
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