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REVIEW

Besilesomab for imaging inflammation and infection in peripheral bone in adults with suspected osteomyelitis

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Abstract: Early and accurate diagnosis of osteomyelitis, an inflammatory process of the bone caused by an infective microorganism, is essential for rapid management of the disease by antimicrobial and/or surgical intervention. Historically, diagnosis has been achieved by histological examination, but, more recently, sophisticated molecular imaging techniques (including computed tomography [CT], magnetic resonance imaging, positron emission tomography, single photon emission CT, scintigraphy) that are increasingly used to support diagnoses made from histological data have been reported. For example, scintigraphy has been used to visualize the inflammatory process *in vivo* using either radiolabeled leukocytes or radiolabeled antigranulocyte monoclonal antibodies (MAbs). Typically, radiolabeling is achieved using technetium-99m (radioactive half-life = 6.02 hours), and the most commonly used MAbs are the Fab fragment of the immunoglobulin (Ig)G antibody directed against the glycoprotein cross-reactive antigen-90 (sulesomab) and an IgG antibody against normal cross-reactive antigen-95 (BW 250/183, besilesomab [Scintimun®]). The aim of the present review is to discuss use of this latter commercially available MAb, besilesomab, for imaging inflammation in adults with suspected osteomyelitis.

Keywords: Scintimun, ^{99m}Tc scintigraphy, radiolabeled monoclonal antibodies, BW 250/183, bone infection

Osteomyelitis

General introduction

Osteomyelitis, an inflammatory process caused by an infective microorganism and accompanied by bone destruction, has been extensively reviewed in the medical literature.[1–6] It can occur in a confined portion of the bone or involve multiple regions, including the marrow, cortex, periosteum, and surrounding soft tissue. Osteomyelitis can be categorized based on its pathological origins, the most frequent being a local spread from a contiguous focus of infection occurring after trauma, surgery, the insertion of joint prostheses or from diabetic foot infection (Figure 1).[1] This form occurs most often in adults and accounts for 80% of cases.[7] Osteomyelitis of hematogenous origin, on the other hand, occurs when bone is seeded by bacteria present in blood and is found mostly in prepubertal children and in elderly patients.[1] Osteomyelitis secondary to vascular insufficiency, in which soft tissue infection in the foot spreads to bone, has also been described in populations with diabetic foot infections.[8] Beyond characterization as contiguous or hematogenous (based on the source of infection), osteomyelitis is also classified as acute or chronic based on its duration.[9] Acute osteomyelitis can be detected by histological methods 2 weeks after the onset of the disease, whereas

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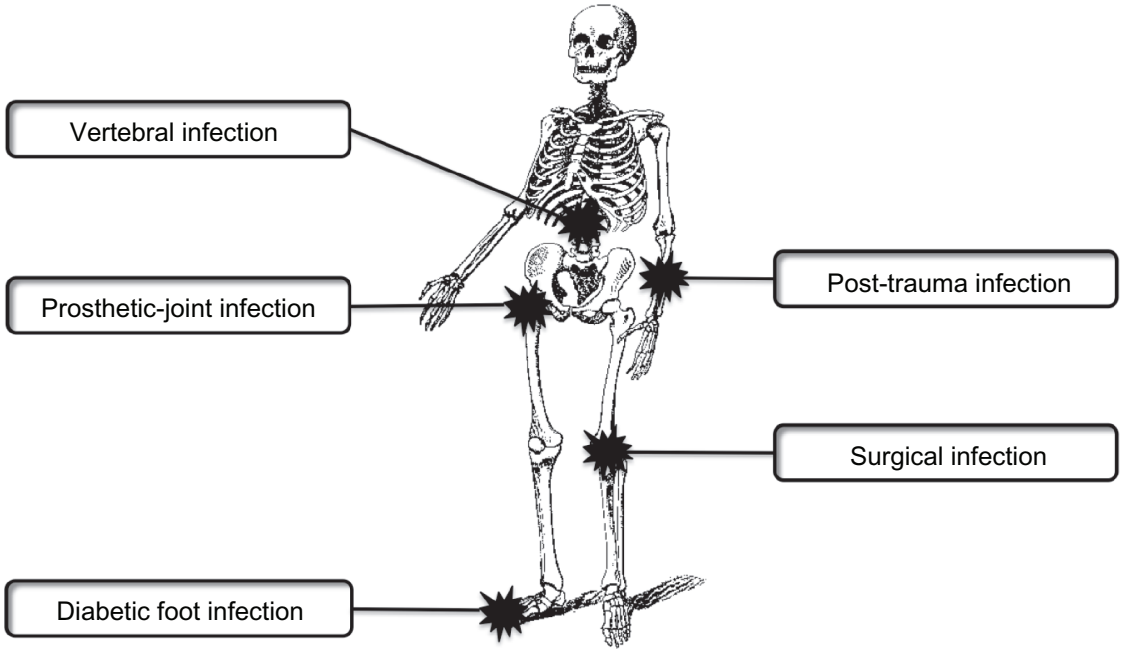


Figure 1 Common causes of osteomyelitis.

chronic osteomyelitis is long standing, evolving over months or years, and is histologically detectable a few months after disease onset. Other classification systems for osteomyelitis include the Waldvogel and the Cierny–Mader schemes.[10,11] The latter is used by orthopedic surgeons for treating patients with chronic osteomyelitis and combines considerations of the anatomical stages of the disease and the physiology of the patient. It applies best to long and large bones and is not very useful in classifying the disease in digits, small bones, or the skull.

Development and progression

Osteomyelitis develops when bacterial contamination and adhesion develop into infection and subsequent chronicity. Pathogenic factors that cause this chronicity can be divided into local and general factors. Local factors include the presence of foreign bodies, bone necrosis, and heavy contamination by devitalized bone fragments from trauma or surgery. Additionally, strains of bacteria may gain a survival advantage from their slow metabolic rates, ability to hide intracellularly, and the presence of a host defect in the presence of an implant.[12] Biofilm-embedded microorganisms have additional advantages, including the resistance to removal tactics, such as the use of antimicrobial or antifouling agents, shear stress, host phagocytic clearance, and host oxygen radical and protease defenses. Biofilms also have the capability to act as diffusion barriers to slow down the infiltration of some antimicrobial agents and could have the potential to detach and spread under mechanical fluid shear or through genetically mediated detachment processes.[13] General factors affecting chronicity in patients include diabetes, peripheral vascular disease, obesity, and smoking.[12]

A typical route for osteomyelitis development begins with the production of pus in the medulla leading to the development of an abscess in the marrow space. This swelling presses against the outer wall of bone, compressing the blood vessels in the bone marrow and leading to localized bone death in avascular areas. Resulting reactive hyperemia is associated with increased osteoclastic activity, leading to localized bone loss and osteoporosis. Progression of this process may lead to bone necrosis and fracture of the affected bone (Figure 2).[1,2]

Diagnosis and treatment

Bone infections are painful and unpleasant for patients and should be treated as early as possible. Acute osteomyelitis responds to treatment with antibiotics alone, although the avascular bone necrosis and sequestrum formation that occur during chronic osteomyelitis may necessitate surgical debridement in addition to antibiotic treatment.[14] Identification of the causative agent of osteomyelitis is essential for administering effective treatment. For example, *Staphylococcus aureus* is the main foreign body found in chronic bacterial osteomyelitis, followed by *Pseudomonas* and Enterobacteriacea.[12,15–18] However, it should be noted that the successful management of most other infectious diseases by antibiotics has not yet

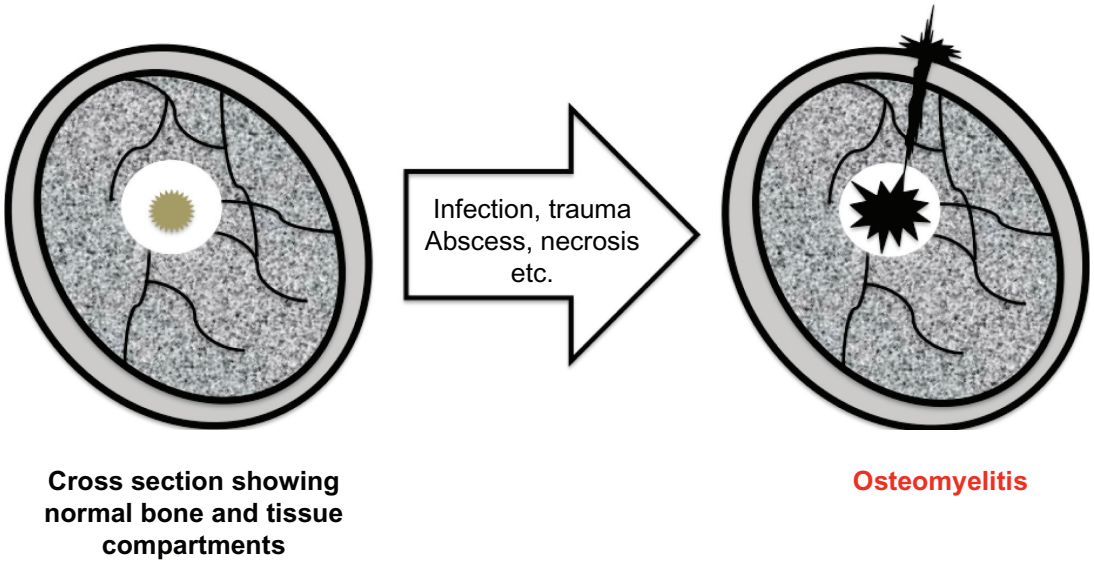


Figure 2 Pathophysiology of osteomyelitis characterized by spread of infection through adjacent soft tissues.

been replicated for osteomyelitis. This is not only due to the unique physiological and anatomical characteristics of bone but also due to difficulties involved in diagnosing osteomyelitis. For example, sometimes osteomyelitis manifests without signs and symptoms. Alternatively, signs and symptoms of osteomyelitis can be difficult to distinguish from other diseases such as neuropathic osteoarthropathy.[19] Moreover, the frequently concurrent existence of bone and soft tissue abnormalities complicates diagnosis of osteomyelitis, leading to false-positive and false-negative findings. Nevertheless, early and accurate diagnosis is essential for successful management of the disease, and so, much research has been undertaken to develop diagnostic molecular imaging strategies to support histological data. Such developments have been the subject of recent reviews.[9,20–25] For example, ultrasound,[26,27] computed tomography (CT),[21,22,28] magnetic resonance imaging (MRI),[29–32] optical[20] and nuclear medicine techniques[20,23,24,33–37] have all been used to improve diagnostic confidence.

Nuclear medicine techniques for diagnosis of osteomyelitis

A range of nuclear medicine techniques (eg, positron emission tomography [PET], single photon emission CT [SPECT] scans, and scintigraphy) have been developed for imaging inflammation and infection and are increasingly used to diagnose osteomyelitis.[20,21,35] For example, fluorine-18 fluorodeoxyglucose ([^{18}F]FDG), a commercially available PET tracer, has shown promise in imaging chronic osteomyelitis. FDG uptake and metabolism are elevated in leukocytes, granulocytes, and macrophages during inflammatory conditions because of increased cellular expression of glucose transporters.[38–40] The numerous advantages of FDG-PET imaging include a higher spatial resolution in comparison to conventional nuclear medicine modalities, fast examination time (result available within 1–2 hours after tracer administration), the ability to differentiate between hematopoietic bone marrow and activated white blood cells (WBCs), and potential application to treatment monitoring.[41] Additionally, the high spatial and contrast resolution of FDG-PET can distinguish soft tissue from osteomyelitis, and the absence of artifacts from metallic implants allows the imaging of patients with suspected infection in hip and knee prostheses.[42–44] A negative result of PET study essentially rules out osteomyelitis because of its high sensitivity in detecting infection; however, this may lead to increased false-positive results.[45,46] A drawback of FDG-PET is the lack of anatomic landmarks, which may make it difficult to assign lesions to a particular structure. Integrated PET-CT scans can be used for functional-morphologic correlation.[39]

The reported sensitivity and specificity for PET diagnosis of osteomyelitis range from 95% to 100% and 86% to 95%, respectively.[46,47] The accuracy of FDG-PET in evaluating prosthetic joint infections, however, is higher in hip prostheses than in knee prostheses, perhaps because attenuation correction in imaging knee prostheses can introduce artifacts that lead to false-positive results.[48] Reported values for sensitivity, specificity, and accuracy of FDG-PET imaging for detecting infections are 90%, 89.3%, and 89.5% for hip prostheses and 90.9%, 72.0%, and 77.8% for knee prostheses, respectively.[49]

Scintigraphy has also been used extensively to image inflammation and infection. For example, in cases looking for peripheral osteomyelitis, triple scintigraphy using technetium-99m (^{99m}Tc)-radiolabeled diphosphonates has historically shown good success in detecting the upregulated bone turnover associated with the disease. For example, ^{99m}Tc-methylene diphosphonate ([^{99m}Tc]MDP) binds to the hydroxyapatite bone crystal, and therefore, signals depend on both blood flow and rates of bone turnover.[50] During triple-phase imaging, positive signs of osteomyelitis are considered through the combined detection of focal hyperfusion immediately following contrast injection, focal hyperemia in the blood pool phase, and focal increases in bone uptake on delayed images.[50] Furthermore, the bone scan can alleviate image artifacts, which are found by CT or MRI in patients with existing implants or prostheses.[9] However, [^{99m}Tc]MDP imaging only denotes regions of active bone turnover and, therefore, cannot discriminate osteomyelitis from other causes of increased local bone remodeling.[9] Therefore, specificity of this technique decreases in patients with underlying skeleton conditions, which may otherwise induce a positive finding on the bone scan.[50] Gallium-67 imaging can be used in conjunction with the bone scan to increase accuracy of detection, but the use of multiple isotopes over several days of imaging can be limiting.[50] Planar scintigraphy can be further improved using 3D SPECT imaging; however, the same caveats regarding specificity still can limit SPECT imaging of [^{99m}Tc]MDP imaging in osteomyelitis.[35]

Inflammation is the body's early response to injury (and infection) and involves delivery of leukocytes to the infected area where they can clear infectious agents and degrade necrotic tissues. Therefore, scintigraphy using *ex vivo* ^{111}In-oxine-radiolabeled leukocytes has been widely used as the gold standard for imaging the inflammation process.[9,21,23,37] The leukocytes are radiolabeled and reinjected into the patient where they become distributed in the intravascular space. Patients then typically receive their scan 4–24 hours postinjection. This lapse gives time for blood pool activity to decrease and improves image quality. An area of increased activity is indicative of inflammation and infection, and Indium-111-labeled leukocyte (^{111}In-L) scintigraphy is the method of choice for localizing osteomyelitis. However, using radiolabeled leukocytes in this capacity also has associated challenges, because there is always the question of whether the radiolabeled cells remain viable and there is also the loss of specificity associated with imaging a system as complicated as the leukocyte response to inflammation. Moreover, *ex vivo* labeling entails cumbersome isolation or reinjection of the cells, and this also involves significant radiation exposure and increased risk of infection to both the patient and the staff.[21,23,51] Therefore, alternative strategies have been developed, including the use of radiolabeled nanocolloids and introduction of radiolabeled antigranulocyte monoclonal antibodies (MAbs), with the aim of addressing some of these issues.

Imaging bone inflammation with ^{99m}Tc-labeled nanocolloids (^{99m}Tc-NCs) offers several advantages over ^{111}In-L scintigraphy, including lower radiation doses, ease of handling, and shorter preparation times. Biodistribution studies of ^{99m}Tc-NCs in the rat have found that the blood activity in bone marrow imaging decreases from 14.5% at 30 minutes, 12.5% at 1 hour, and 12.4% at 3 hours, with 54.5% renal excretion after 24 hours.[52] In a study comparing three human albumin colloids and one antimony sulfide colloid, the nanometer-sized albumin-based colloid labeled with ^{99m}Tc-Nanocoll® (Nycomed Amersham Sorin S.R.L, Saluggia, Italy) had the highest bone marrow or spleen quotient and bone marrow or background quotient in patient scans.[53] Flivik et al[54] found that ^{99m}Tc-NC scintigraphy with this radiopharmaceutical is equivalent to ^{111}In-L scintigraphy with regards to sensitivity, specificity, and accuracy. This study demonstrated a sensitivity of 75% with ^{111}In-Ls and 94% with ^{99m}Tc-NCs. Specificity of 90% was demonstrated with ^{111}In-Ls and 84% with ^{99m}Tc-NCs, whereas diagnostic accuracy was 85% and 87%, respectively. When patients with slightly increased activity were regarded as being negative, the specificity increased to nearly 100%.[54] This is in agreement with a study by Papos et al,[55] which suggests both ^{99m}Tc-NC and ^{99m}Tc-hexamethyl propylene amine oxime – labeled leukocyte scanning were of similar value for the detection of chronic posttraumatic osteomyelitis. However, leukocyte scintigraphy seemed to characterize the grade of inflammation better than did nanocolloid scintigraphy, with good correlation between the leukocyte scanning data and laboratory and bacteriologic data. Another comparative study found nanocolloid and IgG scans have a similar degree of sensitivity (95%) and specificity (100%) in the detection of focal inflammatory processes but are nonspecific in detecting an infective focus.[56] On the other hand, Ooi et al[57] suggest that ^{99m}Tc-NC cannot replace ^{111}In-Ls in the diagnosis of orthopedic infections. In a comparative study involving 19 patients with a high clinical suspicion of infection, the sensitivity was 75% in both methods, and specificities were 79% and 60% for ^{111}In-Ls and ^{99m}Tc-NC, respectively. Additionally, the positive predictive value was 33% with ^{99m}Tc-NC and 50% with ^{111}In-Ls, with three false positives with ^{111}In-Ls scanning and 6 with ^{99m}Tc-NC scanning.[57] It has been suggested that

false positives in nanocolloid scans are due to the suspected localizing mechanism. It is thought that the nanometer-sized particles leak out from the vascular endothelium and basement membrane and enter into the extravascular space and may be taken up into the reticuloendothelial system. In this way, the inflammatory process accounts for the localization of nanocolloid lesions, regardless of the disease etiology.[56,58]

The introduction of radiolabeled MAbs was a step forward in osteomyelitis detection, and this area of research has been the subject of a number of review articles.[23,24] The most commonly used MAbs are the Fab fragment of the immunoglobulin (Ig)G antibody directed against the glycoprotein cross-reactive antigen-90 (sulesomab) and an IgG antibody against normal cross-reactive antigen-95 (NCA-95; BW 250/183, besilesomab [Scintimun®; IBA Molecular Imaging, Dulles, JA]). As besilesomab has marketing approval in Europe,[59] this review will focus upon its use in imaging inflammation and infection to date.

^{99m}Tc-labeled besilesomab

General drug information

Besilesomab (BW 250/183) is a mouse MAb of IgG1 κ isotype against NCA-95. The molecular weight of the antibody is ~150 kDa, and there are two κ-light polypeptide chains (~25 kDa each) and two identical γ1-heavy polypeptide chains (~50 kDa each) that are linked together by disulfide bridges. Besilesomab is radiolabeled with ^{99m}Tc and is marketed as a kit for radiopharmaceutical preparation under the brand name Scintimun.[59] The kit contains the reduced form of besilesomab (ie, disulfide bridges have been prereduced to the corresponding thiols). ^{99m}Tc (radioactive half-life [$t_{1/2}$] = 6.02 hours) is obtained, using a (^{99} Mo or ^{99m}Tc) generator, as [^{99m}Tc]sodium pertechnetate, and this is introduced into the Scintimun kit. The kit contains stannous chloride, which reduces sodium pertechnetate to Tc (IV), and Tc (IV) is then able to bind to the free thiols of the reduced antibody (Figure 3). ^{99m}Tc decays by emission of 140-keV gamma photons to quasi-stable ^{99m}Tc ($t_{1/2} = 2.13 \times 10^5$ years). Besilesomab is able to bind to antigenic structures shared by NCA-95 of granulocytes. Therefore, [^{99m}Tc]besilesomab binds to neutrophils and accumulates at sites of infection and inflammation. These sites appear as corresponding hotspots during scintigraphic imaging, allowing physicians to accurately and noninvasively locate and diagnose infectious and inflammatory lesions. This was a major advance in imaging osteomyelitis, reflected by the number of patients who have received [^{99m}Tc]besilesomab scintigraphy studies (estimated to be >100,000, globally).

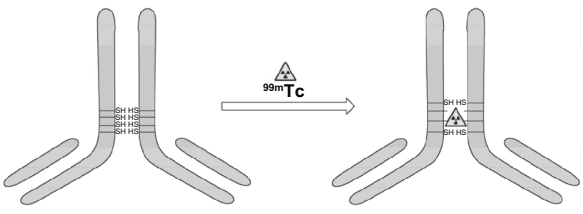


Figure 3 Radiolabeling of besilesomab.

Pharmacological considerations

Extensive pharmacological data for [^{99m}Tc]besilesomab were presented in an assessment report on the evaluation of [^{99m}Tc]besilesomab for human use by the European Medicines Agency (EMEA).[59] The applicant was CIS Bio International and key findings from the EMEA report are concisely presented here for completeness.

Absorption

The pharmacokinetic (PK) profile of besilesomab was evaluated in cynomolgus monkeys after intravenous administration of 0.5 mg antibody/kg of besilesomab with decayed ^{99m}Tc. As expected, serum levels were found to be highest (14.5 µg/mL) at 10 minutes postinjection (n = 2). Subsequently, distribution of the antibody was found to be complete within 20 minutes, and the half-life of the antibody was 31 hours (n = 2). In a related PK study, [^{99m}Tc]besilesomab (2.5 µg antibody and 4–5 MBq ^{99m}Tc) was administered intravenously to rats, and the radioactivity in blood, tissues, urine, and feces was measured at a range of time points between 1 and 48 hours after administration. At 1 hour, the highest levels of radioactivity were found in the blood, followed by the liver, kidneys, compact bone, and small intestine. Elimination from most organs was found to be biphasic (half-lives of the initial and terminal phases were 2–7 and <100 hours, respectively). Plasma half-life was found to be 30–35 hours.

Distribution and dosimetry

Clinical distribution and dosimetry data were obtained throughout a clinical trial of 24 patients with suspected inflammation (open-label, nonrandomized, parallel group design phase I study). Half of the patients received a single intravenous injection of either 0.25 mg (492 MBq) or 1 mg (623 MBq) of [^{99m}Tc]besilesomab. Blood and urine samples for measurement of ^{99m}Tc radioactivity and antibody concentration were taken over 24 hours postinjection. Moreover, additional samples for determination of antibody concentration were taken up to 30 days postinjection. The concentration-time curves obtained in these measurements showed two phases: an early phase (0–2 hours) and a late

phase (5–24 hours). Besilesomab antibody-based half-lives and clearance rates agreed with the corresponding plasma radioactivity values, suggesting that the labeled product was stable *in vivo*. The biodistribution data, measured in this study as percentage of regional activity vs whole body activity, showed similar results for the liver: 1.5% of whole body activity for imaging at 6 hours and 1.6% at 24 hours. The corresponding data for the spleen were 3.0% at 6 hours and 2.3% at 24 hours.

Dosimetry was calculated using the Medical Internal Radiation Dose (MIRD) system and is summarized in Table 1. The effective dose was estimated at 8.63×10^{-3} mSv/MBq of [^{99m}Tc]besilesomab administered to the patient.[59]

Metabolism and excretion

Like most antibodies, besilesomab is metabolized into amino acids during hepatic clearance. Therefore, in addition to the labeled antibody, total blood radioactivity also includes contributions from other radioactive species, such as antibody fragments, metabolites, and free ^{99m}Tc. Each of these by-products is cleared from blood differently. Although the radioactivity associated with intact antibody will stay in the blood for a reasonable time (antibody half-life in plasma = 44.5 hours[59]), metabolites, radioactive fragments, and free ^{99m}Tc will clear more rapidly from blood and will accumulate in the kidneys and, ultimately, in the urine. In all studies, about 14% of the injected radioactivity was recovered in urine, which was only collected for 24 hours after administration. This radioactivity can be attributed to the elimination of free ^{99m}Tc and labeled low-molecular-weight antibody fragments and small radiometabolites. In this report, no information about the fate of the injected radioactivity beyond 24 hours postadministration of [^{99m}Tc]besilesomab was provided. However, the radioactivity absorbed by the kidneys (0.022 mGy/MBq on average) lies in the range of other approved ^{99m}Tc-labeled radiopharmaceuticals.

Table 1 Dosimetry for [^{99m}Tc]besilesomab calculated using the MIRD system[59]

Organ	(mSv/MBq)	
	Reference male	Reference female
Brain	0.00236	0.00312
Heart	0.00495	0.00597
Colon	0.00450	0.00576
Stomach	0.00445	0.00535
Liver	0.00100	0.00126
Small intestine	0.00480	0.00575
Bone marrow (red)	0.00242	0.00229
Muscles	0.00317	0.00391
Ovaries	NA	0.00594
Pancreas	0.00690	0.00826
Skin	0.00178	0.00216
Lungs	0.00125	0.00160
Spleen	0.00271	0.00324
Kidney	0.00210	0.00234
Breast	NA	0.00301
Adrenal	0.00759	0.00937
Testis	0.00182	NA
Thymus	0.00351	0.00423
Thyroid	0.00279	0.00321
Bone	0.00177	0.00227
Uterus	NA	0.00501
Gallbladder	0.00591	0.00681
Bladder	0.00305	0.00380
Whole body	0.00445	0.00552

Note: Effective dose, 0.00863 mSv/MBq.
Abbreviations: ^{99m}Tc, technetium-99m; MIRD, Medical Internal Radiation Dose; NA, not applicable.

Safety profile

A number of genotoxicity studies have been conducted, which conclude that [^{99m}Tc]besilesomab does not show genotoxic potential.[59] Moreover, according to a report submitted to the EMEA, approximately 100,000 patients have received [^{99m}Tc]besilesomab to date. The radiopharmaceutical appears well tolerated, and there have been few reported side effects or adverse events.[59]

Mechanism of action

The mechanism of accumulation of besilesomab at the site of infection and inflammation has not been fully elucidated. However, it has been suggested that it is mainly passive (increased vascular permeability) and partly active (migration of human granulocytes, carrying [^{99m}Tc]besilesomab, to the infection and inflammation sites) because only 10%–20% of the injected radiolabeled antibody bind *in vivo* to human circulating granulocytes. Specific binding of besilesomab to already migrated and activated granulocytes may be the major part of the detection signal.[59] Besilesomab binds granulocytes that express NCA-95, but it has been shown that such binding does not significantly affect granulocyte-mediated functions (eg, enzyme release and pinocytosis).[60] Moreover, besilesomab does not get internalized into the cytoplasm.[61]

Imaging inflammation and infection in patients with suspected osteomyelitis using besilesomab

During the 15 years since the introduction of [^{99m}Tc]besilesomab, numerous clinical studies evaluating its effectiveness in diagnosing osteomyelitis have been reported (Table 2).[29,34,47,59,62–73] These studies have also been the subject of review[20,33,51,74,75] and retrospective data analysis,[29,76] and

Table 2 [^{99m}Tc]Besilesomab imaging in osteomyelitis

Type	N	Dose (MBq)	Scan time (h)	Results	Reference
Suspected peripheral osteomyelitis	55	300–500	2–6; 20–24	sp, 57%; se, 94%; ac, 65%	Ruther et al[67]
Suspected peripheral and central osteomyelitis	57	740	4–6; 24	sp, 92%; se, 88%; ac, NR	Kroiss et al[72]
Suspected chronic osteomyelitis	17	500	4; 24	sp, 100%; se, 100%; ac, NR	Sciuk et al[66]
Suspected peripheral and central osteomyelitis	58	740	3–6; 24	sp, 91%; se, 96%; ac, 93%	Seybold et al[68]
Suspected peripheral and central osteomyelitis	30	500	4; 20–24	sp, 64%; se, 89%	Hotze et al[62]
Suspected peripheral osteomyelitis	8	725	2; 24	sp, 75%; se, 57%; ac, 67%	Peltier et al[70]
Suspected peripheral osteomyelitis	106	300–400	2–4	sp, 93%; se, 69%; ac, 81%	Reuland et al[64]
Chronic posttraumatic peripheral osteomyelitis	24	555	17	sp, 72%; se, 84%; ac, 79%	Kaim et al[65]
Joint prosthesis	57	750	0; 2d–4w	sp, 75%; se, 67%; ac, 73%	Boubaker et al[85]
Suspected peripheral and central osteomyelitis	51	420	4; 24	sp, 77% vs 82%; se, 86% vs 92%; ac, 82% vs 88%	Guhlmann et al[47]
Suspected central osteomyelitis	81	555–925	1; 4; 24	sp, 96%; se, 95%; ac, NR	Gratz et al[71]
Suspected peripheral osteomyelitis	10	740	4–6; 24	NR	Gallowitsch et al[69]
Chronic posttraumatic osteomyelitis	27	750	0; 3–4; 24	sp, 100%; se, 78%; ac, NR%	Horger et al[63]
Phase I trial to determine safety, PK, and diagnostic efficacy	24	0.25 mg[a] 1.0 mg[a]	NR	sp, 88%; se, 100% sp, 93%; se, 100%	CIS Bio International[59]
Phase III trial in patients with inflammatory diseases	690	<400 400–600 600–800 >800	5; 24	sp, 100%; se, 73.5% sp, 94.9%; se, 90.1% sp, 95.7%; se, 90.6% sp, 89.7%; se, 88.8%	CIS Bio International[59]
Phase III trial in patients with suspected peripheral osteomyelitis	119	650–800	4; 24	sp, 69%; se, 76%; ac, NR% Scint: sp, 60%; se 66% Scint + SPECT: sp,	CIS Bio International[59]
Detection of low-grade joint infections	31	NR	5 min; 5; 24	55%; se, 89% Scint + SPECT/CT: sp, 73%; se, 89%	Graute et al[34]

Notes: [a]Dose of radioactivity was not reported but rather injected dose of antibody in mg.
Abbreviations: sp, specificity; se, sensitivity; ac, accuracy; NR, not reported; PK, pharmacokinetic; Scint, [^{99m}Tc]besilesomab scintigraphy; SPECT, single photon emission computed tomography; CT, computed tomography.

the outcome of the body of research suggests that diagnostic accuracy of osteomyelitis using [^{99m}Tc]besilesomab is high.[51] [^{99m}Tc]Besilesomab has also been used to detect inflammation[77] and infection in other diseases, such as diabetic foot,[78,79] fevers of unknown origin,[80] inflammatory bowel disease,[81–83] and septic loosening of knee[84] or hip[85] endoprosthesis, although a detailed discussion of such uses extends beyond the scope of this report. Beyond diagnosis of infection and inflammation, bone marrow scintigraphy has been used to track bone metastases in cancer patients[86,87] and has also been considered for radiotherapeutic applications.[88]

Recently, an assessment report from the EMEA, in response to CIS Bio International's application for marketing authorization, summarizes data from eight separate clinical trials of [^{99m}Tc]besilesomab. For example, a randomized crossover trial, conducted between 2006 and 2008, compared blinded reading of [^{99m}Tc]besilesomab and [^{99m}Tc]WBC images of suspected osteomyelitis (Table 2, entry 16).[59] In this most recent and pivotal phase III trial involving 119 patients with suspected osteomyelitis, the agreement rate between the 2 methods was estimated to be 83% (lower 95% confidence interval limit: 80%); however, there was no adequate standard of truth (or acceptable surrogate) used in this trial, and so diagnostic parameters like sensitivity and specificity could not be calculated. The lack of standard of truth was addressed during post hoc analysis based on a surrogate, which was an evaluation by an expert panel of all data available from the study. The overall diagnostic performance of [^{99m}Tc]besilesomab determined during this post hoc analysis (sensitivity, 76%; specificity, 69%) was similar to that of the previous analysis based on the investigator diagnosis at 1 month (75% and 72%, respectively).

The data presented in Table 2 support clinical trial data from the EMEA report[59] about the apparent relationship between injected dose of [^{99m}Tc]besilesomab and the sensitivity or specificity of the scintigraphy studies. For example, in one of CIS Bio International's clinical trials (Table 2, entry 15), retrospective data analysis factoring in dose

administered to 690 patients confirmed that there was no statistical difference in sensitivity or specificity between the groups receiving different doses of [^{99m}Tc]besilesomab. However, lower sensitivities were observed in this trial for patients who received <400 MBq of [^{99m}Tc]besilesomab, and so, the optimum dose for these studies was set at 400–800 MBq.[59] These data are similar to those reported by Reuland et al[64] (Table 2, entry 7). Reuland et al[64] injected <400 MBq and observed a sensitivity of 69%, although it should be noted that lower sensitivities have also been observed with higher injected doses (eg, Peltier et al[70] reported 57% sensitivity following injection of 725 MBq; Table 2, entry 6).

The results reported from the CIS Bio International's clinical trials are in agreement with other studies reported in the literature (Table 2). For example, in the discussion of advanced experience in diagnosing infections with scintigraphy, Seybold et al[68] examined 58 patients with infection using [^{99m}Tc]besilesomab. Patients were administered ~300 μg of antibody, corresponding to 740 MBq of ^{99m}Tc. In this study, it was reported that sensitivity, specificity, and accuracy were 91%, 96%, and 93%, respectively, and the authors found comparable diagnostic findings to use radiolabeled MAb47. They concluded that [^{99m}Tc]besilesomab had an overall positive predictive value of 97%.

In 1997, Kaim et al[65] explored the use of [^{99m}Tc]besilesomab for imaging chronic posttraumatic osteomyelitis. They compared diagnosis in 24 patients using a [^{99m}Tc]diphosphonate bone scan and MRI, with diagnosis made using the combination of [^{99m}Tc]diphosphonate bone scan and [^{99m}Tc] besilesomab with MRI. The addition of [^{99m}Tc]besilesomab scintigraphy greatly improved diagnostic accuracy. Sensitivity, specificity, and accuracy for the bone scan alone were 92%, 18%, and 58%, respectively, whereas these values were 84%, 72%, and 79% for the combined bone scan and scintigraphy. These results confirm that [^{99m}Tc]besilesomab scintigraphy is a very sensitive, accurate, and reproducible method for evaluating chronic osteomyelitis. However, this study also supports the idea that, when imaging suspected osteomyelitis, diagnostic confidence is improved if a combination of imaging techniques is used rather than a single technique alone. This concept has also been demonstrated by Graute et al[34] in an abstract presented at the 2010 Society of Nuclear Medicine Annual Meeting. In this study, 31 patients had [^{99m}Tc]besilesomab bone scintigraphy carried out at 5 minutes, 5 hours, and 24 hours after injection. Diagnostic sensitivity of the scans was assessed alone and in conjunction with SPECT and SPECT/CT (Table 2, entry 17). The use of [^{99m}Tc]besilesomab bone scintigraphy alone resulted in a specificity of 60% and sensitivity of 66%. Interpreting scintigraphy in conjunction with the SPECT scan resulted in improved sensitivity, whereas specificity was found to be lower (specificity, 55%; sensitivity, 89%). However, marked improvement in both parameters was observed when scintigraphy data were interpreted with SPECT and CT (specificity, 73%; sensitivity, 89%). Similar data were reported for [^{99m}Tc]besilesomab by Horger et al[63] in their 2003 study and for [^{99m}Tc]diphosphonate by Wuest et al.[36,89]

Nevertheless, there are challenges to evaluating osteomyelitis with [^{99m}Tc]besilesomab. Typically, these include false-positive and false-negative diagnoses. For example, less encouraging results were reported by Hotze et al[62] in 1992 when 20 patients with suspected peripheral osteomyelitis and 10 patients with suspected infection of the spine were scanned with [^{99m}Tc]besilesomab. Patients received 500 MBq of [^{99m}Tc]besilesomab and were scanned at 4 hours and 20–24 hours postinjection. In many cases, the scan was successful in revealing osteomyelitis. For example, the scan shown in Figure 4 was taken for a patient with a history of arthrodesis of the right ankle joint and subsequent chronic pain. The scan suggests infection, and indeed, in this case, chronic osteomyelitis was confirmed by biopsy.

However, of the 20 patients with suspected peripheral osteomyelitis, four false-positive and one false-negative findings were also observed, giving a specificity of 64% and sensitivity of 89%. These false-positive and false-negative results support the conclusions of a number of groups that scintigraphy is a powerful tool when used in conjunction with other modern imaging modalities, such as MRI or CT, and histologic examinations.[9,29,76]

Finally, Guhlmann et al[47] compared [^{99m}Tc]besilesomab antibody scintigraphy (patients were scanned 4 and 24 hours



Figure 4 Image of chronic osteomyelitis obtained using [^{99m}Tc]besilesomab. Copyright © 1992, Society of Nuclear Medicine. Reprinted with permission from Hotze AL, Briele B, Overbeck B, et al. Technetium-99m-labeled anti-granulocyte antibodies in suspected bone infections. *J Nucl Med*. 1992;33:526–531.

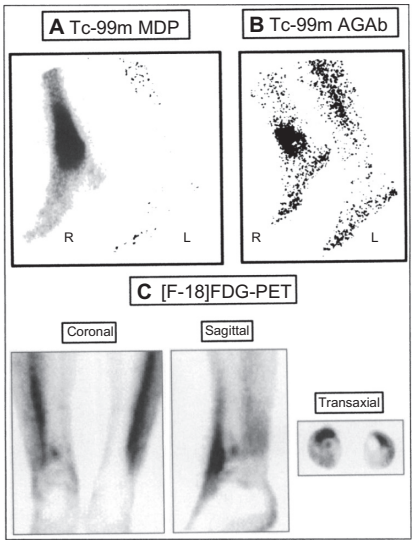


Figure 5 A comparison of [^{99m}Tc]besilesomab, [^{99m}Tc]MDP, and [^{18}F]FDG-PET imaging of osteomyelitis. Copyright © 1998, Society of Nuclear Medicine. Reprinted with permission from Guhlmann A, Brecht-Krauss D, Suger G, et al. Fluorine-18-FDG PET and technetium-99m Antigranulocyte Antibody Scintigraphy in Chronic Osteomyelitis. *J Nucl Med*. 1998;39:2145–2152.
Abbreviations: ^{99m}Tc, technetium-99m; MDP, methylene diphosphonate; AGAb, antigranulocyte antibody; R, right; L, left; [^{18}F]FDG-PET, fluorine-18 fluorodeoxyglucose positron emission tomography.

after administration of 0.3–0.5 mg/420 MBq of MAb) with [^{18}F]FDG-PET imaging (patients were scanned 50 minutes after administration of 320 MBq of [^{18}F]FDG) for detection of chronic osteomyelitis (Figure 5). Fifty-one patients who previously had a [^{99m}Tc]MDP bone scan were investigated, and two expert readers analyzed the data. They concluded that although both methods were suitable for diagnosis of chronic osteomyelitis in the peripheral skeleton, FDG-PET was superior (accuracy, 96% vs 96%; sensitivity, 100% vs 97%; and specificity, 95% vs 95%) to [^{99m}Tc]besilesomab (accuracy, 82% vs 88%; sensitivity, 86% vs 92%; and specificity, 77% vs 82%). The main difference between the two imaging agents in this study was that FDG allowed more reliable distinction between osteomyelitis and infection of the surrounding soft tissue.

Conclusion

Antigranulocyte scintigraphy with radiolabeled MAbs has proven a reliable method for diagnosing osteomyelitis. One such antibody, [^{99m}Tc]besilesomab, is commercially available, and over 100,000 patients have received a scan with this agent. [^{99m}Tc]Besilesomab has proven effective for determining the location of inflammation and infection in peripheral bone in adults with suspected osteomyelitis. However, at the time of writing, there are currently no criteria to distinguish infection and inflammation by means of [^{99m}Tc]besilesomab imaging. The reported data suggest that the sensitivity of [^{99m}Tc]besilesomab is equivalent to that of [^{99m}Tc]WBCs but specificity is lower. A lower specificity is considered acceptable because it has been shown that diagnostic confidence can be significantly improved when [^{99m}Tc]besilesomab is used in conjunction with other appropriate imaging modalities, such as bone scans or SPECT/CT imaging.

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Disclosure

The authors report no conflicts of interest in this work.

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