Comparison of technetium 99m polyclonal human immunoglobulin and technetium 99m monoclonal antibodies for imaging chronic osteomyelitis

First clinical results

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Abstract. The accuracy of technetium-99m human immunoglobulin (HIG) for the detection of chronic osteomyelitis (OM) was compared with white blood cell scintigraphy using 99mTc-labelled monoclonal mouse antibodies (MAB). Seventeen patients suspected of having OM in 20 lesions went through three-phase skeletal scintigraphy, HIG scintigraphy and MAB scintigraphy. The final diagnosis was established by open surgery, histology and bacteriology. Chronic OM was proved in 14/20 lesions. Six of these 14 infections were located in peripheral areas without active bone marrow and 8/14 in central areas with active bone marrow. In peripheral OM, 5/6 with HIG and 6/6 with MAB were true positives. In the central skeleton all 8/8 infections appeared as cold lesions in the MAB study, which were defined as being false negative due to their non-specificity. Using HIG, 5/8 central infections were determined to be truly positive by showing photon-rich lesions. These 5 lesions were located in the hip region and in the pelvis, whereas 3 lesions of the spine were missed. There were no false-positive results in either studies. In conclusion, MAB was superior to HIG in peripheral OM concerning sensitivity, anatomical landmarks and differentiation of soft tissue versus bone infection. In central OM MAB detected all lesions accurately, but no differential diagnosis was possible due to the non-specificity of photon-low areas. In this respect HIG seems to be more specific due to the increased accumulation even in central infection sites.

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Introduction

In imaging chronic osteomyelitis (OM) the assessment of disease activity, disease extent and the differential diagnosis are the main questions to be answered. While acute and subacute courses often lead to characteristic clinical and concordant imaging results, the diagnosis of chronic recurrent or low-grade OM may create problems.

In addition to the highly sensitive, but non-specific three-phase bone scan (technetium-99m methylene diphosphonate: 99mTc-MDP) several more specific imaging modalities are available in nuclear medicine: gallium-67-citrate, 99mTc-labelled colloids, indium 111-labelled oxinate or 99mTc-hexamethylpropylene amine oxime (HMPAO)-labelled autologous leucocytes and 99mTc- or iodine-123-labelled murine monoclonal antibodies. A new attempt in scintigraphic imaging of infection is the use of 111In-labelled polyclonal, non-specific human immunoglobulin (HIG), which first was described by Fischman et al. (1987, 1988a–d) and Rubin et al. (1988, 1989a, b). However, extra-osseous infections were the main subject of these publications.

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A comparative study using $^{111}$In-labelled HIG and $^{111}$In-labelled autologous leucocytes in bone infections and joint disorders was presented by Oyen et al. (1990). $^{99m}$Tc-HIG was investigated by Buscombe et al. (1990) in patients with different sites of inflammation, including some cases with osteomyelitis. The aim of this study was the evaluation of $^{99m}$Tc-labelled HIG, especially in the diagnosis of chronic OM in comparison to $^{99m}$Tc-labelled monoclonal mouse antibodies (MAB).

**Materials and methods**

**Radiopharmaceuticals.** Technescan HIG (MDH-67), (Mallinckrodt Diagnostica, The Netherlands) is a one-vial kit, which contains 1 mg of modified non-specific polyclonal human IgG, 8 µg stannous chloride as reductant and sodium tartrate as transfer ligand. The IgG is pretreated with 2-iminotriathanol in order to enable direct labelling with $^{99m}$Tc (Goedemans and Panek 1989). Labelling was performed according to the manufacturers instructions by adding up to 555 MBq pertechnetate in a volume of 0.5 ml to the vial. After incubation for 20 min at room temperature and dilution to a volume of 4 ml with saline, the labelling yield was determined by gel filtration using PD10 columns (Pharmacia, Freiburg, FRG). The column was saturated prior to the analysis of $^{99m}$Tc-HIG with a solution of human serum albumin to avoid non-specific protein binding. Radiochemical yields between 97% and 99% have been observed. The final solution was checked for clarity prior to the injection.

Scintimun Granulozyt (Behringwerke AG, Frankfurt/Main) is a murine monoclonal antibody (BW 250/183), which binds to NCA-95 on human granulocytes. For direct labelling with $^{99m}$Tc (Goedemans and Panek 1989), the antibody is reduced with a thiol agent, treated with 0.5 mg 1,1,3,3-propane tetraphosphonic acid and 24 µg stannous chloride and then labelled by the addition of 1 GBq $^{99m}$Tc-pertechnetate (Schwarz and Steinsträßer 1987). The amount injected into the patients was 500 MBq containing 0.5 mg of the antibody.

**Patients and imaging modalities.** In a prospective study we examined 25 patients with clinically suspected chronic OM. Pregnancy and an age less than 18 years were exclusion criteria. The study was approved by the local ethics committee; written consent was obtained. The final diagnosis was established by open surgery, histology and bacteriology.

All patients underwent quantitative three-phase bone scan ($^{99m}$Tc-MDP), which was positive in 21 cases. Seventeen of these 21 patients were investigated with MAB and HIG scintigraphy. The interval between these investigations was 2 to 4 days. For MAB and HIG scintigraphy about 500 MBq (437–555 MBq) of the radiopharmaceutical was injected slowly i.v. Digital (10 min, 256 × 256 matrix) and analogue (600 kcounts in the central body, 400 kcounts in the extremities) planar spot images of the suspected area in at least two projections were obtained at 4 and 24 h p.i. (GE, MAXI 37, LEHR collimator). Additionally, anterior and posterior whole-body scans were performed with a double-head gamma camera (Siemens, whole-body scan, LEHR collimator) within 15 min.

If the lesion was located in the spine or pelvis, SPECT (360° rotation, 5.6° increments, 30 s/projection, 64 × 64 matrix) was performed (GE, MAXI 400 ACT, LEGP collimator). The digital data were quantified by determination of the infection to non-infection (I/NI) ratio. This ratio was defined in the three phases of the bone scan and the 4- and 24-h scans of HIG and MAB scintigraphy. In some cases in the HIG study, no exact ROI could be defined and therefore quantification was impossible. These difficulties occurred especially in studies of the axial skeleton (lack of anatomical landmarks, overlapping blood pool activity or lack of focal increased activity). In the MAB study cold lesions were not quantified and were defined as being false-negative due to their non-specificity.

Visual assessment of the scans was done by three experienced nuclear physicians/radiologists (J.S., P.B., O.S.) without knowledge of other diagnostic results. The intensity of local activity accumulation in HIG and MAB scintigraphy was qualitatively classified into five groups: − = no accumulation, + = minor accumulation, + + = moderate accumulation, + + + = intense accumulation, cl = cold lesion (Table 1).

**Results**

In 25 patients with clinically suspected chronic OM, the delayed phase of the bone scan was positive on 21 occasions. Seventeen of these 21 patients were investigated with HIG and MAB scintigraphy and form the basis of the study. Out of 20 suspicious lesions in these 17 patients 14 were proven to be chronic OM by surgery, histology and cultures. Eight infectious lesions were located in areas with active bone marrow (spine, n = 3; pelvis and hips, n = 5) and six in areas without active bone marrow (lower extremities). In 12/14 OM the causative microorganism was *Staphylococcus aureus* and in two cases of spondylitis, *Mycobacterium tuberculosis*. In the 6 remaining lesions surgery, histology and cultures showed no evidence of infection.

The results of HIG and MAB scintigraphy (Tables 2, 3) require separate consideration of lesions in areas with active bone marrow (n = 10) from those in areas without active bone marrow (n = 10). In the periphery 9/10 lesions had concordant findings in HIG and MAB scintigraphy. Four of four non-infectious lesions were demonstrated to be truly negative in both studies, while the MAB study classified 6/6 OM and the HIG study 5/6 OM as truly positive. The one case missed by HIG was a low active chronic OM of the tibia (specificity: 100% for both studies; sensitivity: 100% MAB, 83.3% HIG). Using a 95% confidence interval and the Fisher test, the higher sensitivity of MAB was significant.

Lesions in central areas (n = 10) where active bone marrow is present showed different morphological activity features in MAB and HIG scintigraphy. In the MAB study all cases of infectious (n = 8) and non-infectious disease (n = 2) led to a non-specific cold lesion due to depression of the bone marrow (sensitivity: 0%). In contrast, HIG scintigraphy showed increased activity in 5/8 infectious sites that were classified as true positives (sensitivity: 62.5%). These lesions were located in the hip and pelvis (Fig. 3), while the three infections of the spine showed no abnormal activity distribution and were therefore missed with HIG (Fig. 2). The difference in sensitivity between MAB and HIG was found to be stat-