Diagnosis of Bone, Joint, and Joint Prosthesis Infections with In-111-labeled Nonspecific Human Immunoglobulin G Scintigraphy

The diagnostic accuracy of scintigraphy performed after injection of indium-111-labeled nonspecific human immunoglobulin G (IgG) was studied in 113 patients with 120 foci of suspected infection in bone (52 chronic and eight acute infections), joints (15 localizations), joint prostheses (37 prostheses), and soft tissue of the locomotor system (eight localizations). All patients also underwent standard three-phase scintigraphy after injection of technetium-99m-labeled methylene diphosphonate. A scan obtained with In-111-labeled IgG was considered positive if focal increasing accumulation was noted over time. In 51 patients (45.1%), the results of scintigraphy were verified with intraoperative cultures, and in 21 patients (18.6%), with needle aspiration. The prevalence of infection was 59%; overall sensitivity, 97%; and specificity, 85%. Use of In-111-labeled IgG enabled correct identification of the presence, site, and extent of infection in 69 of 71 proved foci of infection; 41 of 48 negative studies were correct. Only two infections proved with culture were missed; in both patients, the cultures revealed growth of Staphylococcus aureus in low counts.

Accurate noninvasive diagnosis of infection in bones, joints, and joint prostheses remains a vexing clinical problem. All widely used radiographic and scintigraphic techniques have limitations. Radiography has poor results in assessment of disease activity in osteomyelitis (1). Technetium-99m methylene diphosphonate (MDP) studies show excellent results in ruling out infection, but specificity is low (2,3). Reports on the use of gallium-67 scintigraphy are variable, but apparently it is less well suited for imaging infection because of its accumulation in areas of bone remodeling and physiologic excretion in the intestines (4). In chronic low-grade infections, decreased sensitivity of labeled white blood cell (WBC) scintigraphy has been reported (5). Initial results of a study on the usefulness of scintigraphy performed after administration of indium-111-labeled human nonspecific polyclonal immunoglobulin G (IgG) indicated the possibilities of a new, convenient technique for imaging infection (6). In our study we assessed the results of In-111-labeled IgG scintigraphy in patients with infections of bones, joints, joint prostheses, and soft tissues of the locomotor system.

Materials and Methods

Radiopharmaceutical Doses

Human nonspecific polyclonal IgG, sterile and pyrogen-free monomeric IgG (Sandoglobulin; Sandoz, Nuremberg, Germany), was conjugated to diethylene-triaminepentaacetic acid (DTPA) bicyclic anhydride (bicyclic DTPA) according to the method described by Hnatowich et al (7) and labeled with In-111 (indium chloride; Amersham International, Buckinghamshire, England). The labeling efficiency was always higher than 95%. A dose of approximately 1 mg of IgG labeled with 75 MBq of In-111 was administered intravenously by means of bolus injection.

For therapeutic purposes, nonlabeled IgG has been used in gram doses for more than 20 years with an excellent safety record. In more than 800 patient studies, both in our department and at the Massachusetts General Hospital in Boston, no adverse reactions after injection of 1 mg of IgG radiolabeled with 75 MBq of In-111 were observed (6) (W.J.G.O., unpublished data, 1991).

Imaging Procedures

One hundred twenty foci of suspected infection were studied in 113 patients, who also underwent standard three-phase scintigraphy after injection of Tc-99m MDP. In-111-labeled IgG was injected either 2-7 days after Tc-99m MDP skeletal scintigraphy had been completed or after the second-phase Tc-99m-MDP scintigrams were obtained. Scintigrams were obtained with a gamma camera (Orbiter; Siemens Gammasonics, Hoffman Estates, IL) connected to a commercially available image processor (Scintview, Siemens Gammasonics).

At 4, 18-24, and 42-48 hours after injection of In-111-labeled IgG, gamma camera images were obtained for a preset time of 5, 7.5, and 10 minutes, respectively, with a medium-energy collimator. In most cases the gamma camera was set for both the 173- and the 247-keV photopeak with symmetric 15% windows. Typical count rates in the trunk region ranged from 1.0 million to 1.5 million counts; in the pelvic region, from 600,000 to 750,000 counts; and in the lower limb, from 80,000 to 150,000 counts.

When In-111-labeled IgG was injected shortly after the second phase of bone scanning, only the 247-keV peak was used to acquire In-111-labeled IgG images 4 and 18-24 hours after injection to avoid

Abbreviations: DTPA = diethylene-triamine-pentaacetic acid, IgG = immunoglobulin G, MDP = methylene diphosphonate, WBC = white blood cell.
scatter of Tc-99m MDP on gamma camera images obtained with In-111-labeled IgG. No significant scatter of In-111 was observed in the Tc-99m-MDP scintigrams.

**Image Interpretation**

All images were interpreted by three observers (W.J.G.O., R.A.M.J.C., F.H.M.C.) blinded to the results of the verification procedures. The images obtained with In-111-labeled IgG were interpreted with the corresponding bone scintigram. The Tc-99m-MDP scintigrams were used to localize osseous structures, joint arthroplasties, or both. However, the presence or absence of infection was estimated with In-111-labeled IgG scintigraphy only. A scan obtained with In-111-labeled IgG was considered positive if focal increasing accumulation was noted over time. Nonvisualization of a suspected lesion or failure to show increasing accumulation on the scan was considered a negative finding.

**Patient Categories and Verification Procedures**

The patients were categorized on the basis of the nature of the suspected focus of infection: chronic osteomyelitis, infection of total hip prosthesis, infection of total knee prosthesis, acute osteomyelitis or spondylodiskitis, arthritis, or soft-tissue infection. For example, if a patient had chronic osteomyelitis with soft-tissue extension, this patient's case was categorized as chronic osteomyelitis. Whenever evidence of infection persisted for less than 6 months, or even years, the infection was regarded as chronic. Several patients had more than one joint prosthesis. Only the results of the In-111-labeled IgG scintigraphy of prostheses suspected of being infected are included in the Table.

In 51 patients (45.1%), the results of scintigraphy were verified by means of intraoperative cultures and in 21 patients (18.6%) by needle aspiration with subsequent Gram stains and cultures. In 26 patients (23.0%), 22 of whom had negative findings on scintigrams obtained with In-111-labeled IgG, verification was obtained with the Tc-99m MDP scintigrams. In four of the culture-proved infectious lesions (8%), other causative microorganisms or a mixed flora were cultured.

Seven studies showed accumulation of In-111-labeled IgG in lesions that proved to be noninfected (Table, "FP" column). In two of these patients, In-111-labeled IgG was accumulated near the neck of femoral component of a cemented total hip prosthesis.

**RESULTS**

All patients had increased uptake of Tc-99m MDP on the bone scintigrams. All infections of joint prostheses were chronic. Nonsymptomatic prostheses with a normal appearance on radiographs never showed increased uptake of In-111-labeled IgG.

The Table shows the overall results of In-111-labeled IgG scintigraphy in the various categories, based on the results of the verification procedures.

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of Lesions</th>
<th>TP</th>
<th>TN</th>
<th>FP</th>
<th>FN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic osteomyelitis</td>
<td>52</td>
<td>37</td>
<td>14</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Infection of total hip prosthesis</td>
<td>31</td>
<td>7</td>
<td>21</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Infection of total knee prosthesis</td>
<td>6</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Acute osteomyelitis or spondylodiskitis</td>
<td>8</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Infectious arthritis</td>
<td>15</td>
<td>11</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Soft-tissue infection</td>
<td>8</td>
<td>7</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>120</strong></td>
<td><strong>70</strong></td>
<td><strong>41</strong></td>
<td>7</td>
<td><strong>2</strong></td>
</tr>
</tbody>
</table>

**Note.**—FN = false-negative for infection; FP = false-positive for infection; TN = true-negative for infection; TP = true-positive for infection.

**Figure 1.** Right total hip prosthesis infected with *S. aureus* in a man aged 81 years. (a) Scintigram obtained with In-111-labeled IgG (posterior view, obtained 48 hours after injection, with a preset time of 10 minutes and 600,000 counts) shows increased uptake of radionuclide around the prosthesis, with soft-tissue extension of infection (arrow). L = left, R = right. (b) Plain radiograph shows nonspecific osteolysis of a bone graft at the lateral margin of acetabular component but no evidence of infection such as femoral osteolysis.
In one patient, noninfected, necrotic, fibrinoid tissue was removed at surgery; in the other pat-
tient, active periarticular ossifications accounted for the false-positive find-
ings at scintigraphy with In-111-labeled IgG. A hemorrhage in the total knee
prosthesis of a patient with hemophilia and a hematoma after bi-
opsy for chondrosarcoma in another patient caused uptake of In-111-la-
beled IgG. In two patients with suspected infectious arthritis of the knee,
findings on scintigrams obtained with In-111-labeled IgG were positive,
while an infectious origin could not be proved: One patient had severe,
rapidly progressive degenerative os-
teoarthritis, and the other patient, sterile synovitis. The seventh patient
with false-positive scintigrams ob-
tained with In-111-labeled IgG
showed increased uptake at the ven-
tral side of a total knee prosthesis. At
surgery, prepatellar bursitis was
found. The bursa was removed. Sub-
sequent cultures remained negative.

The prosthesis itself appeared normal
on the scintigrams. Results of this
study were falsely positive for soft-
tissue infection.

Only two infections proved with
culture were missed: one case of low-
grade hematogenous osteomyelitis in
the intertrochanteric region and one
infected cemented total hip prosthesis
(Table, "FN" column). In both pa-
tients the intraoperative cultures re-
vealed growth of S aureus in low
counts.

In this group of 120 suspected in-
fec tious foci with a prevalence of in-
f ection of 59\%, the sensitivity for the
detection of infection was 97\% and
the specificity for infection, 85\%, with
a positive predictive value of 88\% and
a negative predictive value of 95\%.

Figures 1–3 are typical examples of
scintigrams obtained with In-111-
labeled IgG. Figure 1 shows the scinti-
gram and radiograph from a patient
with an infected total hip prosthesis
with extension of the infection in the
soft tissue near the neck of the femo-
r al component of the prosthesis. Fig-
ure 2 shows a scintigram and radiog-
raph of a patient with chronic
osteomyelitis of the femur. Figure 3
shows the scintigrams of a large soft-
tissue abscess of the upper leg.

Four patients with a suspected fo-
cus of infection and three other pa-
tients also had abnormalities of non-
inf ectous origin (lesions not tabulated
in the Table). Four recent noninfected
fractures up to 4 weeks old without
complications were positive on scinti-
grams obtained with In-111-labeled
IgG. In contrast, two noninfected frac-
tures 4–6 months old, without compli-
cations, that were clearly visible on
the Tc-99m MDP images showed no
accumulation of In-111-labeled IgG. A
hemangioma showed some uptake of
the radionuclide on the images ob-
tained 4 hours after injection but was
considered negative for inflammation,
because In-111-labeled IgG did not
further accumulate in the lesion on
the subsequent images.

DISCUSSION

Our results indicate a high sensitiv-
ity of scintigraphy performed after
injection of In-111-labeled IgG for the
detection of infections in bones,
joints, and joint prostheses. In our
study only two low-grade S aureus
infections were missed. The 85\% spec-
ificity for infection was lower than the
sensitivity. This is not surprising, be-
cause labeled IgG is a nonspecific ra-
diopharmaceutical that accumulates
not only in infection but also in vari-
ous other types of inflammatory pro-
cesses (6,8,9). In our study this is illus-
trated by the images categorized as
false-positive. In all seven of these
cases, an inflammatory component
could be identified. In some patients
with joint prostheses, wear of the
prosthetic components may cause a
foreign-body reaction that causes for-
mation of granulation tissue (10). If
this sterile inflammatory reaction is
substantial, it could cause false-posi-
tive findings on scintigrams obtained
with In-111-labeled IgG. In general,
aseptic loosening of a prosthesis re-
tulted in positive Tc-99m-MDP bone
scans, but the images obtained with
In-111-labeled IgG were unremark-
able. Findings on scintigrams ob-
tained with In-111-labeled IgG were
positive in four recent noninfected
fractures.

Accumulation in sterile inflamma-
tory lesions has also been reported
after administration of other radiopharmaceuticals such as Ga-67 and
labeled WBC scintigraphy (11–13).

No consensus exists in the radiol-
yogy literature on the utility of Ga-67
in infectious bone and joint disease.
Some authors presented rather poor results due to accumulation of Ga-67 in noninfected areas with increased bone turnover (14,15). Accuracy might improve with use of sequential Tc-99m-MDP and Ga-67 scintigraphy (16,17). The characteristics of Ga-67 have additional disadvantages: multi-peak, high-energy photon emission, which is less suited for imaging, and physiologic intestinal excretion (9). This excretion does not interfere with image quality in the limbs, of course, but it may obscure mild uptake in the lumbar and lower thoracic spine.

A relatively new radiopharmaceutical for evaluation of musculoskeletal infection is Tc-99m-nanocolloid. Although good results are obtained in acute infection, Tc-99m-labeled nanocolloid appears to be of limited value in the evaluation of the prosthetic joint (18).

The results of scintigraphy performed after administration of In-111-labeled WBCs in chronic infection are also variable. Some authors report excellent results (13,19,20). Others find relatively low sensitivity in low-grade infection (5,15). Initial results of Buscombe et al (9) indicate a similarity in performance between In-111-labeled WBCs and Tc-99m-labeled IgG in 16 patients with osseous infection. In a comparative study of In-111-labeled WBCs and In-111-labeled IgG, we found a significantly better performance of In-111-labeled IgG on scintigrams (21). Recently, Palestro et al (22) reported the efficacy of In-111-labeled WBCs and Tc-99m-labeled sulfur colloid in sequential imaging of bone marrow to detect infection of total hip prostheses. The usefulness of WBCs labeled with Tc-99m hexamethyl-propyleneamine oxime in scintigraphy of infectious bone and joint disease is not well established, but it is likely that the performance is similar to that of WBCs labeled with In-111. In a small group of patients, Roddie et al (23) reported good results with Tc-99m-labeled WBCs in scintigraphy. WBC scintigraphy shows high sensitivity and specificity in acute infection, especially when the patient's WBC count is elevated (5). Our study indicates that scintigraphy performed with In-111-labeled IgG also yields good results in low-grade infection when the 48-hour imaging protocol is used. In acute infection, accurate imaging is possible within 24 hours whenever images are obtained 4 and 24 hours after injection.

In addition to low sensitivity in low-grade infection, the need for cell labeling facilities is another drawback for the widespread use of labeled-leukocyte scintigraphy. Moreover, isolation and labeling of WBCs is time-consuming and expensive and thus makes instantaneous preparation impossible. The IgG-DTPA conjugate is readily available as a sterile, pyrogen-free kit for rapid labeling without the need to handle blood of patients. This is especially valuable in acute infection, when results of scintigraphy should be available in the shortest possible time. In acute infection it is possible to make an accurate diagnosis with In-111-labeled IgG scintigraphy within 24 hours after referral to the nuclear medicine department.

Evaluation of chronic osteomyelitis with radiographs is difficult due to lack of accuracy (1,16). Magnetic resonance imaging could be an important modality for obtaining additional information in this group of patients (16).

Although the exact mechanism of accumulation of In-111-labeled IgG in foci of infection remains to be elucidated, we conclude that scintigraphy performed with In-111-labeled IgG is a valuable technique for the evaluation of infection in bones, joints, and joint prostheses. Because infection of the spine was studied in few patients, further studies are needed to fully elucidate the role of scintigraphy performed with In-111-labeled IgG in infections of the axial skeleton.

One has to remember that In-111-labeled IgG, like all other radiopharmaceuticals used for imaging infection, accumulates in any inflammatory focus, regardless of whether the focus is infectious or sterile. However, in chronic recurrent low-grade infection, which is one of the major indications for scintigraphy performed with In-111-labeled IgG, this distinction is of minor importance, because a sterile inflammation in these areas is less likely to occur. In our experience, uptake of In-111-labeled IgG due to sterile inflammation, such as repair after recent fracture and wound healing after surgical procedures, disappears after 4–6 months. Until then, prudent interpretation of scintigrams obtained with In-111-labeled IgG is necessary to avoid false-positive results.

References
7. Hnatowich DJ, Childs RL, Lanteigne D, Najafi A. The preparation of DTPA-coupled antibodies radiolabeled with metallic...