**Original**

99mTc-HMPAO labelled white blood cell scintigraphy in the diagnosis and monitoring of response of the therapy in patients with active bronchiectasis

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**ABSTRACT**

**Aim:** The aim of this study was to assess the role of labelled leukocyte scintigraphy in the diagnosis and monitoring of response to therapy of patients with active bronchiectasis.

**Material and methods:** Twenty patients underwent 99mTc-Technetium hexamethylpropyleneamine oxime (99mTc-HMPAO) labelled white blood cell (WBC) scintigraphy. A second scintigraphy was performed in 13 patients at 10 day of the treatment. Regional 99mTc-HMPAO WBC uptake and radiologic imaging findings (high resolution computed tomography or Chest X-Ray) in the lungs were classified into 3 categories in 6 lung areas. Scintigraphic, radiological and clinical disease scores were calculated for all patients.

**Results:** An abnormal accumulation was visually observed in 19 of 20 patients on the pre-treatment scans, the scintigraphy showing 95% sensitivity. A significant difference was found between early and late ratios (P = 0.001) in the pre-treatment scans. The infected areas revealed a significant decrease in uptake ratios on the post-treatment scans compared to the pre-treatment scans (P = 0.001). However, no significant correlation was determined between clinical and radiological scores, clinical and scintigraphic scores and also between scintigraphic and radiological scores (P > 0.05).

**Conclusions:** 99mTc-HMPAO WBC scintigraphy may be a useful tool to evaluate response to therapy in patients with active bronchiectasis.

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**Gammagrafía con leucocitos marcados con 99mTc-HMPAO en el diagnóstico y monitorización de la respuesta al tratamiento en pacientes con bronquiectasias activas**

**Resumen**

**Objetivo:** El objetivo de este estudio fue evaluar el papel de la gammagrafía con leucocitos marcados en el diagnóstico y monitorización de la respuesta al tratamiento en pacientes con bronquiectasias activas.

**Material y métodos:** Se realizó una gammagrafía con leucocitos marcados con 99mTc-Tecnecio hexametilpropilenoamina oxima (99mTc-HMPAO). Una segunda gammagrafía de control se efectuó en 13 pacientes a los 10 días del tratamiento. La captación regional de los leucocitos 99mTc-HMPAO y los hallazgos de la imagen radiológica (tomografía computarizada de alta resolución o la radiografía de tórax) en 6 zonas pulmonares se clasificaron en 3 categorías. Se calcularon índices gammagráficos, radiológicos y clínicos de actividad o captación en todos los pacientes.

**Resultados:** Se observó visualmente una acumulación leucocitaria patológica en 19 de 20 pacientes en el estudio pretratamiento, con una sensibilidad del 95% de la gammagrafía. Se encontró una diferencia significativa entre los índices precoces y tardíos (p = 0.001) en la exploración pretratamiento. Las áreas infectadas mostraron una significativa disminución de ratios de captación en la gammagrafía post-tratamiento respecto a la exploración preterapia (p = 0.001). Sin embargo, no se encontró una correlación significativa entre las puntuaciones de valoración clínica y radiológica, clínica y gammagráfica, y tampoco entre las puntuaciones de la gammagrafía y los radiológicos (p > 0.05).

**Conclusiones:** La gammagrafía con 99mTc-HMPAO leucocitos puede ser una herramienta útil para evaluar la respuesta al tratamiento en pacientes con bronquiectasias activas.

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**Introduction**

Bronchiectasis is a respiratory disorder characterized by chronic sputum production, recurrent exacerbations and, in some cases, progressive lung destruction. It is a chronic disorder that can result in significant physical and social morbidity. The commonly observed features are abnormally dilated thick-walled bronchi, microbial infection, and a persistent inflammatory response that is accompanied by the release of immune mediators and microbial toxins.\(^1\)

In patients with bronchiectasis, high resolution computed tomography (HRCT) has proven to be a reliable diagnostic method...
for detection of infection spread and for localization and characterization of areas of parenchyma or bronchial abnormality throughout the lungs.\textsuperscript{2,3} 99m-Tc-Technetium hexamethylpropyleneamine oxime (\textsuperscript{99m}Tc-HMPAO) labelled white blood cell (WBC) scintigraphy was described by Peters et al 20 years ago.\textsuperscript{4} Since then, it has been used in the diagnosis of a wide variety of inflammatory diseases such as bone infections, inflammatory bowel diseases, abdominal infections and pelvic inflammatory disease.\textsuperscript{5–9} However, there is only a single publication in the literature about the diagnostic role of \textsuperscript{99m}Tc-HMPAO-WBCs in patients with bronchiectasis.\textsuperscript{10}

The aims of the present study were to determine the efficacy of \textsuperscript{99m}Tc-HMPAO-WBC scintigraphy in detecting the actively infected lung areas in patients with bronchiectasis, as well as to assess the impact on monitoring response to therapy and predicting disease recurrences by scintigraphic imaging.

Materials and methods

Patients

Twenty consecutive patients (10 males, 10 females) ranging in age from 38 from 77 years (mean age: 58 ± 13) were analyzed in this prospective study. Patients with clinical evidence of exacerbation and radiologically proven bronchiectasis affecting one or more lung segments were included in this study. An exacerbation was defined as persistent (> 24 hour) deterioration in at least three respiratory symptoms (cough, dyspnea, haemoptysis, increased sputum purulence or volume, and chest pain), with or without fever (> 37.5°C), radiographic deterioration, systemic disturbances, or deteriorating chest examination signs.\textsuperscript{11}

The exclusion criteria were: 1) the diagnosis of cystic fibrosis or allergic bronchopulmonary aspergillosis; 2) unexpected chest radiography findings; 3) active mycobacterium tuberculosis or atypical mycobacterial infections; 4) a history of renal disease or cancer; 5) pregnancy or breast-feeding. The Local Ethics Committee approved this investigation, and each patient gave informed consent prior to participation to the study.

Clinical assessment and treatment

Patients were asked to score severity of cough as 0, 1, 2, 3, or 4 corresponding to “no, very mild, mild, moderate and severe cough” respectively, using a visual analogue chart, and a dyspnea score was assessed similarly.\textsuperscript{12} Sputum purulence score was expressed as 0, 1, 2, 3, 4, 5 and 6 corresponding to “no, transparent, opaque and milky white, grey, pale green, moderately green and dark-green sputum” respectively.\textsuperscript{13} Clinical disease score was calculated from each of the 20 patients using the sum of scores of severity of cough, dyspnea and sputum purulence.

Amoxicillin–clavulunate (875 mg amoxicillin + 125 mg clavulunate, b.i.d.) was prescribed empirically for exacerbations of bronchiectasis for outpatient management. Parenteral treatment (piperacillin-tazobactam + amicasin) was given to patients in need of hospitalization with acute respiratory failure. The duration of the treatment was 10 days. A stable clinical condition was defined as the absence of clinical criteria of an exacerbation (impairment of respiratory symptoms with an increase in the volume, change in the macroscopic characteristics of sputum, or fever).

Radiological imaging and assessment

Chest X-ray and HRCT were performed during the first 3 days of acute exacerbation. Chest X-ray was repeated following a 10-day treatment course. The numbers of the bronchiectatic lung lobes were determined from HRCT scans performed for each patient. The presence and the extent of bronchiectasis in each lobe were graded using a scale from 0 to 2 where 0: no bronchiectasis, 1: non-segmental disease and 2: segmental disease. Both lungs were divided into 3 areas in order to obtain compatibility with the scintigraphic images (right upper, right middle, right lower, left upper, left middle and left lower). The total radiological score for each patient was calculated by sum of the disease scores of previously mentioned 6 lung areas.

Scintigraphic imaging and analysis

All patients underwent planar chest scans before the antibiotic therapy. In addition, 13 patients underwent a second scan 10 days after the treatment. Anterior and posterior planar images of the chest were acquired 45 minutes (early phase) and 2 hours (late phase) after intravenous injections of \textsuperscript{99m}Tc-HMPAO-WBCs. The separation of WBCs and the labelling procedure with \textsuperscript{99m}Tc-HMPAO were performed according to the consensus report.\textsuperscript{14} The administered dose was 296 ± 78 (163–378) MBq, depending on the labelling efficacy. All images were obtained using a dual-head gamma camera (E-cam; Siemens Inc., Erlangen, Germany) with low-energy-general-purpose collimators.

Scintigraphic images were visually and semiquantitatively assessed by an experienced nuclear medicine physician who was unaware of results of the clinical or radiological examinations. Both lungs were divided into 3 areas similar to radiological images for visual and semiquantitative assessment.

Regional \textsuperscript{99m}Tc-HMPAO WBC uptake in the lungs was visually classified into three categories: 0) no focal or diffuse increased uptake in the regions of lungs; 1) lesions with focal, non-segmental...
uptake; 2) lesions with diffuse segmental uptake. Using these 3 categories visual scintigraphic scores were calculated.

For semiquantitative analysis, a rectangular region of interest (ROI) was drawn around the site of increased $^{99m}$Tc-HMPAO leukocyte uptake over the abnormal lung areas and the right axillary region, to obtain background uptake. The average counts per pixel in the abnormal lung areas were divided by average counts per pixel in the axillary to calculate the lesion/non lesion activity ratio (Fig. 1). Visual scintigraphic results were compared with those of the HRCT or chest X-Ray findings prior to treatment on a patient-by-patient basis.

**Data analysis**

Conventional methods were used to generate descriptive statistics. The results of early and late scintigraphic ratios, and pre and post-therapy scintigraphic ratios, were compared with paired Wilcoxon test. A comparison of the scintigraphic ratios taken from the responder and non-responder groups was carried out using the Mann–Whitney U-test. Spearman’s rank test was used to calculate the correlation between results of scintigraphic, radiological and clinical assessments. P values less than 0.05 were considered to be statistically significant.

**Results**

Twenty patients were recruited for the first step of this study (pre-treatment assessment). Thirteen patients completed the second step (post-treatment assessment). Five patients did not return for follow-up clinical control during the study period and the remaining 2 patients did not agree to have a second scan after the treatment. In all patients, clinical and radiological recovery was monitored after 10 days treatment period. Demographic data, results of pre and post-therapy clinical, radiological and scintigraphic scores and post-treatment scintigraphic findings of all patients were shown in Table 1.

The sensitivity of $^{99m}$Tc-HMPAO WBC scintigraphy was found to be 95% for the diagnosis of bronchiectasis exacerbation. Evaluation of 120 lung areas (20 patients x 6 areas) was carried out by using radiological and scintigraphic methods. The number of total infected areas was found 53 by radiological evaluation, but 84 areas was described scintigraphically. The uptake ratios were calculated in these areas in early and late images semi-quantitatively and mean ± SD of these ratios were found 6.07 ± 2.66 and 3.65 ± 1.35, respectively. A significant difference was found between early and late ratios ($P=0.001$).

However, there were not significant correlations between clinical score and radiological and scintigraphic scores of the patients (radiological $R=0.41$, $P=0.06$; scintigraphic $R=0.31$, $P=0.17$). Similarly, no significant correlation between scintigraphic scores and radiological scores was determined ($R=0.27$, $P=0.24$).

Scintigraphy was performed on only 13 patients 10 days after the treatment period. According to results of the visual and semi-quantitative analysis of the scintigraphic images, 4 of these patients showed no pathological uptake (complete response), and 6 of them had diminished uptakes (partial response). The remaining 3 patients demonstrated increased uptake on one or more affected areas when compared to the pre-treatment images. These 3 patients were scintigraphically accepted as non-responders. There were recurrences in all of 13 patients who had post-treatment scintigraphic images. Although all 3 scintigraphically non-responding patients showed clinical recurrences, 5 of 10 scintigraphically complete or partial responders demonstrated clinical response (3 of partial, 2 of complete responders) in first 3 months of follow-up period. In addition, during 1 year follow-up period, 18 of 20 cases of pre-treatment group showed 1 to 3 recurrences.

Table 1

<table>
<thead>
<tr>
<th>Name</th>
<th>Sex/Age</th>
<th>Disease Type</th>
<th>Pre-treatment Clinical score (0-14)</th>
<th>Radiological Score (0-12)</th>
<th>Scintigraphic Score (0-12)</th>
<th>Post-treatment Clinical score (0-14)</th>
<th>Post-treatment Scintigraphic Finding</th>
<th>Recurrence (first 3 months)</th>
<th>Recurrence rate (in first year follow-up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-BS</td>
<td>F/53</td>
<td>Cystic</td>
<td>11</td>
<td>4</td>
<td>10</td>
<td>4</td>
<td>CR</td>
<td>YES</td>
<td>2</td>
</tr>
<tr>
<td>2-FY</td>
<td>F/57</td>
<td>Cystic</td>
<td>14</td>
<td>4</td>
<td>11</td>
<td>4</td>
<td>CR</td>
<td>NO</td>
<td>1</td>
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<tr>
<td>3-GK</td>
<td>F/49</td>
<td>Cylindric</td>
<td>11</td>
<td>5</td>
<td>11</td>
<td>3</td>
<td>CR</td>
<td>NO</td>
<td>2</td>
</tr>
<tr>
<td>4-OG</td>
<td>M/60</td>
<td>Cystic</td>
<td>14</td>
<td>6</td>
<td>7</td>
<td>3</td>
<td>CR</td>
<td>YES</td>
<td>3</td>
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<tr>
<td>5-ME</td>
<td>M/70</td>
<td>Cylindric</td>
<td>13</td>
<td>4</td>
<td>7</td>
<td>6</td>
<td>PR</td>
<td>NO</td>
<td>1</td>
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<td>F/38</td>
<td>Cystic</td>
<td>14</td>
<td>6</td>
<td>11</td>
<td>3</td>
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<td>3</td>
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<tr>
<td>7-HB</td>
<td>F/52</td>
<td>Cystic</td>
<td>14</td>
<td>2</td>
<td>11</td>
<td>4</td>
<td>PR</td>
<td>YES</td>
<td>3</td>
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<tr>
<td>8-HK</td>
<td>M/48</td>
<td>Cystic</td>
<td>14</td>
<td>7</td>
<td>9</td>
<td>6</td>
<td>PR</td>
<td>NO</td>
<td>1</td>
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<tr>
<td>9-BA</td>
<td>M/77</td>
<td>Cylindric</td>
<td>10</td>
<td>2</td>
<td>6</td>
<td>5</td>
<td>PR</td>
<td>NO</td>
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<tr>
<td>10-NA</td>
<td>F/42</td>
<td>Cylindric</td>
<td>11</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>PR</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td>11-HC</td>
<td>F/60</td>
<td>Cystic</td>
<td>13</td>
<td>8</td>
<td>5</td>
<td>6</td>
<td>NR</td>
<td>YES</td>
<td>3</td>
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<tr>
<td>12-SE</td>
<td>M/71</td>
<td>Cystic</td>
<td>13</td>
<td>7</td>
<td>9</td>
<td>4</td>
<td>NR</td>
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<td>1</td>
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<tr>
<td>13-NK</td>
<td>F/46</td>
<td>Cystic</td>
<td>8</td>
<td>6</td>
<td>9</td>
<td>3</td>
<td>NR</td>
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<td>2</td>
</tr>
<tr>
<td>14-AK</td>
<td>M/52</td>
<td>Cystic</td>
<td>11</td>
<td>2</td>
<td>4</td>
<td>NA</td>
<td>NA</td>
<td>YES</td>
<td>2</td>
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<tr>
<td>15-MK</td>
<td>F/70</td>
<td>Varicose</td>
<td>13</td>
<td>3</td>
<td>6</td>
<td>NA</td>
<td>NA</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td>16-FS</td>
<td>F/65</td>
<td>Varicose</td>
<td>12</td>
<td>2</td>
<td>7</td>
<td>NA</td>
<td>NA</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td>17-SG</td>
<td>M/84</td>
<td>Varicose</td>
<td>10</td>
<td>3</td>
<td>7</td>
<td>NA</td>
<td>NA</td>
<td>NO</td>
<td>0</td>
</tr>
<tr>
<td>18-DA</td>
<td>M/74</td>
<td>Varicose</td>
<td>13</td>
<td>5</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>YES</td>
<td>1</td>
</tr>
<tr>
<td>19-MB</td>
<td>M/66</td>
<td>Cystic</td>
<td>13</td>
<td>5</td>
<td>8</td>
<td>NA</td>
<td>NA</td>
<td>YES</td>
<td>3</td>
</tr>
<tr>
<td>20-AG</td>
<td>M/40</td>
<td>Cylindric</td>
<td>8</td>
<td>2</td>
<td>2</td>
<td>NA</td>
<td>NA</td>
<td>NO</td>
<td>0</td>
</tr>
</tbody>
</table>

CR: complete responder; NA: not available; NR: non-responder; PR: partial responder.

**Discussion**

Patients with bronchiectasis commonly expectorate viscous, mucopurulent and infected sputum. If this condition is not effectively treated, chronic respiratory infections can then result in cellular necrosis and airway lesions that contribute significantly...
Table 2
Pre-treatment and post-treatment early and late phase images uptake ratios for patients who had post-treatment scintigraphic imaging, and statistical results for the groups.

<table>
<thead>
<tr>
<th></th>
<th>Before Therapy (n = 13, a = 62)</th>
<th>After Therapy (n = 13, a = 62)</th>
<th>After Therapy (complete and partial response) (n = 10, a = 49)</th>
<th>After Therapy (not-response) (n = 3, a = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early Scan (45 min) Ratios</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>6.15 ± 2.57</td>
<td>4.14 ± 2.45</td>
<td>3.70 ± 2.13</td>
<td>5.79 ± 2.92</td>
</tr>
<tr>
<td>P value</td>
<td>0.0001</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Late Scan (2 h) Ratios</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>3.59 ± 1.11</td>
<td>2.69 ± 1.35</td>
<td>2.36 ± 1.06</td>
<td>3.92 ± 1.64</td>
</tr>
<tr>
<td>P value</td>
<td>0.0001</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a: number of pathological lung areas; n: number of patients.

To morbidity. Early antibiotic therapy for suspected exacerbations in patients with bronchiectasis would probably limit this vicious cycle.15,16

The excellent performance of leucocytes radiolabelled with 99mTc-HMPAO for imaging infection and inflammation has been demonstrated previously in numerous studies.17 In these reports, sensitivity of radiolabelled leucocyte scintigraphy exceeded 95% for detecting infectious/inflammatory foci. When 99mTc-HMPAO WBCs are compared to 111In WBCs, patients are exposed to lower radiation doses and waiting period for imaging after injection is significantly shorter. Therefore, this procedure should be preferred for use in children and in cases requiring immediate results.18,19 Infectious or inflammatory foci can be detected as early as 30 minutes following the injection of 99mTc-HMPAO WBCs.5,20 This non-invasive imaging technique also makes it possible to distinguish acute bacterial infection from inactive disease or other infections such as those caused by viral, mycobacterial, or fungal pathogens.21

While labelled leukocyte scintigraphy with 111In or 99mTc-HMPAO WBC is commonly used for assessment of skeletal and abdominal infections or inflammations, there has been only a limited number of investigations on its use in diagnoses of lung infections. Roddie et al first demonstrated 99mTc-HMPAO WBC uptake in patients with bronchiectasis. 99mTc-HMPAO WBC were used in diagnosing 100 patients with 6 different infectious or inflammatory diseases, but only seven patients with bronchiectasis were included in their study.10 Currie et al showed an accumulation of 111In labelled granulocytes in the respiratory tracts of patients with bronchiectasis.22 In their study, images obtained at 24 h after injection revealed segments showing 111In accumulation at active disease areas. In the same study, correlations were found between the elimination of 111In from the body, the 24-hour sputum volume and lesion extension on computed tomography. Another study conducted by Jones et al, performed on patients with lobar pneumonia and bronchiectasis, showed active sequestration of 111In labelled.
leukocytes in 4 of 5 patients with bronchiectasis. However, in the same study, FDG uptake was not observed in these patients and this result was thought to be indicative of neutrophil migration.\textsuperscript{23}

Initial sequestration of labelled leucocytes in normal lungs has been reported after intravenous administration, with subsequent rapid clearance of the activity from the lungs.\textsuperscript{18} Similarly, diffuse and faint uptake was observed in normal lung areas in our patients. In our study, heterogeneously increased radiopharmaceutical uptakes were found at the infection areas and these were much higher than physiological in both early and late scans.

Some studies performed on abdominal or skeletal infection sites have reported progressively increasing radiopharmaceutical uptake in infection areas in the late scans.\textsuperscript{24–26} In contrast, in the present study, the uptake rate in infected areas of the lung in the late images was decreased compared to that seen in the early images. Removal of labelled leukocytes from the infection area by high blood flow in the lungs was assumed as the underlying reason for this finding. Thus, we suggest that imaging performed at the 45\textsuperscript{th} min. after injection may be adequate for assessing lung infections by $^{99m}$Tc-HMPAO WBC scintigraphy. Later images may create the possibility of false negative evaluations.

In the present study, pathological WBC uptake was determined to be higher than that rated by radiological methods. Moreover, more than half of the areas that were radiologically believed to have a localized disease were determined to manifest diffuse characteristics by scintigraphy. Increased pathological uptake in areas with active disease on scintigraphic images can be semiquantitatively measured, and changes occurring in those areas after treatment can be monitored. However, there were not any correlation among clinical, scintigraphic and radiological scores in our study. The parameters of clinical score are related to inspection and examination of patients themselves whereas radiological and scintigraphic scores are calculated by assessment of imaging findings. On the other hand, we did not find any correlation between scintigraphic and radiological scores. We think that scintigraphic scores are more effective than radiological indices for evaluation of the active inflammatory process in the pulmonary parenchyma maybe because radiological findings cannot easily distinguish acute exacerbation signs from sequela.

Recurrences and therapy response are commonly determined by observing changes in clinical findings of patients with bronchiectasis. Clinical findings may not be reliable predictors of recurrence, which is a common problem for bronchiectasis. However, according to our results, $^{99m}$Tc-HMPAO WBC scintigraphy may have the potential not only for diagnosis of bronchiectasis, but also for predicting recurrences during follow-up. Additionally, our study findings may predict the relationship between possibility of recurrences and post-treatment scintigraphic findings in the follow-up period of patients with bronchiectasis.

The main difficulty encountered with the use of labelled leucocytes with $^{99m}$Tc-HMPAO is the need for in vitro isolation of blood components, which can expose the patient and laboratory technicians to the hazards of infection and cause long labelling times. In addition, another limitation of WBC scintigraphy is that it is very expensive. In our country, $^{99m}$Tc-HMPAO WBC scintigraphy is 8 times more expensive than HRCT.

A limitation of our study is that SPECT-CT was not used in this patient series. We believe that multimodal systems can be much more effective to understand imaging findings of underlying active infectious and the pathophysiology of inflammatory processes.

In conclusion, $^{99m}$Tc-HMPAO WBC scintigraphy may be a helpful tool to evaluate therapy response of patients with active bronchiectasis. However, results of a newly arranged study using SPECT-CT may be more beneficial to understand the differences between scintigraphic and radiological findings.

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**References**