

## Clearance of inhaled $^{99m}\text{Tc}$ -DTPA predicts the clinical course of fibrosing alveolitis

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*Clearance of inhaled  $^{99m}\text{Tc}$ -DTPA predicts the clinical course of fibrosing alveolitis. A.U. Wells, D.M. Hansell, N.K. Harrison, R. Lawrence, C.M. Black, R.M. du Bois. ©ERS Journals Ltd 1993.*

**ABSTRACT:** The aim of this study was to determine whether the speed of technetium-labelled diethylene-triamine-pentacetate ( $^{99m}\text{Tc}$ -DTPA) clearance from the lung is predictive of disease progression in fibrosing alveolitis, as judged by changes in respiratory function tests.

82 nonsmoking patients with fibrosing alveolitis were studied (progressive systemic sclerosis, n=53; lone cryptogenic fibrosing alveolitis, n=29).

Normal  $^{99m}\text{Tc}$ -DTPA clearance at initial measurement predicted stable disease; rapid  $^{99m}\text{Tc}$ -DTPA clearance identified patients at risk of deterioration. Repeat measurement of clearance, approximately 12 months later, enabled the definition of a subgroup at higher risk, with persistently abnormal  $^{99m}\text{Tc}$ -DTPA clearance, and a smaller subgroup in whom reversion of clearance to normal was associated with a sustained improvement in respiratory function indices. These findings were not attributable to differences in treatment between subgroups.

We conclude that the speed of  $^{99m}\text{Tc}$ -DTPA clearance discriminates between stable and progressive disease in fibrosing alveolitis.

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In interstitial lung disease, active inflammation in the lower respiratory tract results in lung injury and fibrosis; logically, the detection of persistent inflammation should identify patients at greater risk of deterioration. Clearance of inhaled technetium-labelled diethylene-triamine-pentacetate ( $^{99m}\text{Tc}$ -DTPA) from the lung is a measure of epithelial permeability [1] and is abnormal in several interstitial lung diseases; it has been used as a marker of alveolar inflammation in sarcoidosis [2] and extrinsic allergic alveolitis [3].  $^{99m}\text{Tc}$ -DTPA clearance is also abnormal in fibrosing alveolitis associated with systemic sclerosis [4], a condition in which the histological appearances of lung disease are identical to those of lone cryptogenic fibrosing alveolitis (CFA) [5].

The prevalence of CFA is increasing; in the United Kingdom, current mortality rates are likely to exceed 1400 per year [6]. There is evidence that treatment prolongs survival in patients with less extensive fibrosing alveolitis [7]. However conventional therapies have a high incidence of side effects; for this reason, treatment is often delayed until symptoms have increased, by which time considerable irreversible lung damage has often occurred. A diagnostic technique which correctly predicts progressive disease, thereby justifying treatment before the patient has become disabled, would be a significant advance in the management of fibrosing alveolitis.

In this study, we evaluated the predictive value of measurements of  $^{99m}\text{Tc}$ -DTPA clearance in identifying subsequent trends in respiratory function tests (RFT) in CFA and fibrosing alveolitis associated with systemic sclerosis. Normal  $^{99m}\text{Tc}$ -DTPA clearance was indicative of stable disease; persistently abnormal  $^{99m}\text{Tc}$ -DTPA clearance identified patients at risk of deterioration.

### Material and methods

#### Patients

82 patients who had undergone  $^{99m}\text{Tc}$ -DTPA clearance measurement were studied. Hospital case records of all patients and death certificates of the 10 patients who died were examined. 29 had lone CFA (age 54±15 years, 18 males), diagnosed on clinical criteria used in a previous study [7], with the addition of physiological criteria, as follows: 1) no history of exposure to a fibrogenetic agent; 2) the presence of persistent bilateral crackles; 3) the presence of bilateral abnormalities compatible with pulmonary fibrosis, on chest radiography; 4) restriction in lung volumes or an isolated defect in carbon-monoxide diffusing capacity. The diagnosis was confirmed by open lung biopsy in 22 out of 29 cases; in the remaining seven cases, abnormalities typical of fibrosing alveolitis were seen on thin section computed tomography (CT) [8].

Fifty three patients fulfilled the American Rheumatism Association (ARA) preliminary criteria for systemic sclerosis [9] (age  $49 \pm 12$  years, 14 males) and had evidence of fibrosing alveolitis either on open lung biopsy ( $n=35$ ) or on CT of the lungs ( $n=18$ ). Patients with systemic sclerosis were referred to our unit with established or suspected lung involvement from systemic sclerosis.

CT scans of the lungs were reviewed by a single observer. In all cases, appearances were considered to be typical of fibrosing alveolitis [10, 11], a disease in which CT has a high diagnostic accuracy [12, 13].

Exclusion criteria consisted of: 1) connective tissue diseases other than systemic sclerosis, including mixed connective tissue diseases; 2) malignancy involving the lungs; 3) current smoking (within 6 months of the measurement of clearance). Bronchoalveolar lavage fluid was routinely examined for appearances typical of smoking; 4) Duration of follow-up from first  $^{99m}\text{Tc}$ -DTPA scan less than six months.

The study was approved by the local Ethics Committee.

#### *$^{99m}\text{Tc}$ -DTPA clearance*

Clearance of aerosolised  $^{99m}\text{Tc}$ -DTPA from lungs to blood was measured as previously described [14]. An aerosol of  $^{99m}\text{Tc}$ -DTPA was produced using an Acorn nebuliser and administered for 4 minutes; the particle size was limited to less than  $2 \mu\text{m}$ . One-minute frames were acquired by a gamma camera for 45 min; background subtraction was employed, using activity in the central abdomen (not including the kidneys). An exponential fit was derived from the first 15 min of the curve (starting from peak activity) and the half-time of clearance was obtained; slow and fast components were not delineated by curve-stripping. The normal range for  $^{99m}\text{Tc}$ -DTPA clearance was defined in 22 nonsmoking volunteers (values lying within two standard deviations of the mean figure) [4]; on this basis, a clearance half-time of less than 40 min was regarded as abnormal. A clearance half-time of less than 20 min (50% of normal) was categorised as very rapid. Patients were divided into those with abnormal clearance (Group A) and those with normal clearance (Group N) at initial measurement. A further subdivision was made, in patients undergoing a second measurement of clearance, on the basis of trends in clearance, into the following categories: persistently abnormal clearance (subgroup AA), abnormal clearance which reverted to normal (subgroup AN), persistently normal clearance (subgroup NN) and normal clearance reverting to abnormal (NA).

#### *Respiratory function tests*

In all patients, RFT (expressed as percentages of predicted values based on age, sex, height and ethnic origin) [15] had been performed within 4 weeks of initial and, where applicable, repeat  $^{99m}\text{Tc}$ -DTPA clearance measurement. RFT were repeated at regular intervals until the end of follow-up (a minimum of 6 months after the

first  $^{99m}\text{Tc}$ -DTPA scan in all patients and 6 months after the second scan in patients in whom clearance measurement was repeated).

#### *Treatment*

Details of treatment of fibrosing alveolitis were obtained from the hospital case records. Treatment was defined as corticosteroid therapy with or without an immunosuppressive agent (cyclophosphamide, azathioprine or cyclosporin A).

#### *Statistical analysis*

The data were collected prospectively and analyzed retrospectively; the decision as to the method of analysis was taken prior to the examination of lung function trends. Changes in total gas transfer (DLCO) and forced vital capacity (FVC) were evaluated; a significant change was defined as an increase or decrease of 15% of the absolute values at initial measurement. RFT trends between first measurement of clearance and the end of follow-up were tabulated; the frequency of increase and decrease of DLCO and/or FVC was compared for group A versus group N and in subgroups AA, AN and NN. Differences in RFT trends between groups were assessed using the chi-squared test, or the Fisher exact test when the sample size was too small for the chi-squared approximation to hold. Differences in mean data between subgroups was evaluated using Student's *t* test. Results are expressed as mean  $\pm$  SD.

### **Results**

Initial clearance was abnormal (rapid) in 59 out of 82 patients (group A, 72%: systemic sclerosis,  $n=37$ : CFA,  $n=22$ ) and normal in 23 out of 82 patients (group N, 28%: systemic sclerosis,  $n=16$ : CFA,  $n=7$ ). Mean follow-up, from initial measurement of clearance to the last measurement of RFT, was  $26.2 \pm 11.9$  months; follow-up did not differ significantly between patients with rapid clearance ( $25.6 \pm 12.3$  months) and those with normal clearance ( $27.3 \pm 10.9$  months), or between CFA ( $23.2 \pm 12.4$  months) and systemic sclerosis ( $27.8 \pm 11.3$  months).

Rates of  $^{99m}\text{Tc}$ -DTPA clearance are shown in Fig. 1. The range of findings was similar in the two diseases. However, clearance half-time was very rapid (*i.e.*  $<20$  min) more frequently in CFA (12/29, 41%) than in systemic sclerosis (8/53, 15%),  $p < 0.001$ . A similar percentage of patients with CFA (7/29, 24%) and systemic sclerosis (15/53, 30%) had normal clearance at first measurement.

#### *Predictive value of a single measurement of $^{99m}\text{Tc}$ -DTPA clearance*

To determine whether a single measurement of clearance was predictive of change in physiological measures, RFT trends from initial measurement of clearance until the end of follow-up were related to clearance speed; these trends are depicted in Fig. 2.

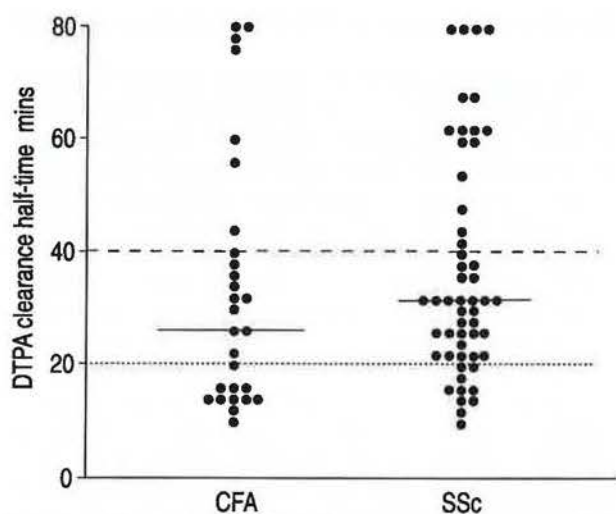


Fig. 1. - The speed of <sup>99m</sup>Tc-DTPA clearance, expressed as the half-time of clearance, in patients with systemic sclerosis (SSc), compared with patients with cryptogenic fibrosing alveolitis (CFA) (median values indicated by bar). Values above the broken line lie within the normal range (>40 min); values below the dotted line were characterised as "very rapid". Clearance half-time was very rapid in 41% of patients with CFA, but in only 15% of patients with systemic sclerosis, p<0.001.

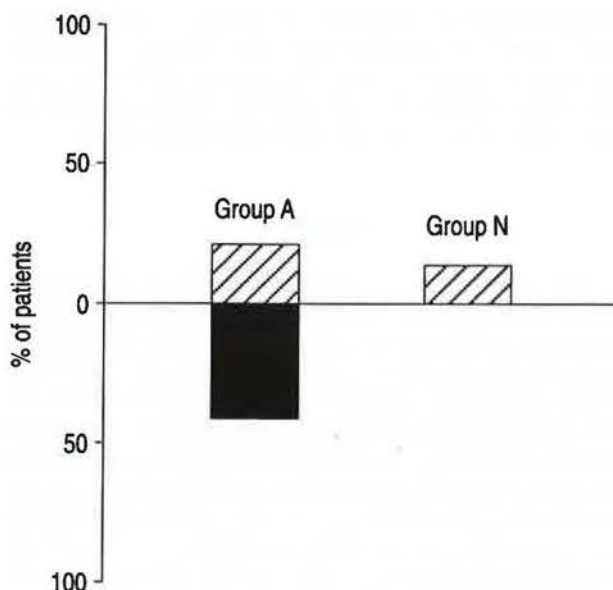


Fig. 2. - The percentage of patients with improvements (▨) or declines (■) in respiratory function tests (RFT) from initial measurement of <sup>99m</sup>Tc-DTPA clearance related to clearance speeds. Deterioration in RFT was confined to group A, p<0.001. Group A: abnormal clearance at first measurement; group N: normal clearance at first measurement).

In 40/82 there was a significant change (either decline or improvement) in RFT; change was seen more frequently in DLCO (33/82) than in FVC (24/82).

In patients with rapid clearance (group A), a decline in RFT was seen in 25/59 (43%; CFA, n=13; systemic sclerosis, n=12). In marked contrast, deterioration in RFT was not observed in any of the 23 patients with normal clearance (group N), p<0.001; this difference was significant both in systemic sclerosis (p<0.002) and in

CFA (p<0.005). In patients with rapid clearance, a decline in RFT occurred more frequently in CFA (13/22, 59%) than in systemic sclerosis (12/37, 32%), p<0.05.

The frequency of significant improvement in RFT during follow-up did not differ significantly between group A (20%; CFA, n=4, systemic sclerosis, n=8) and group N (13%; CFA, n=1, systemic sclerosis, n=2) at initial measurement.

*Baseline RFT, initial <sup>99m</sup>Tc-DTPA clearance and changes in RFT*

Baseline RFT in relation to concurrent <sup>99m</sup>Tc-DTPA clearance is shown in Table 1. Mean DLCO and FVC were more severely depressed in group A than in group N, in both CFA and systemic sclerosis. However, there was a considerable overlap; abnormal clearance was seen in 20/35 patients with normal FVC values and 1/7 patients with normal DLCO values, whereas normal clearance was seen in 8/47 patients with abnormal FVC values and in 17/75 patients with abnormal DLCO values.

Baseline RFT were not consistently predictive of progression of disease. In patients who deteriorated, the initial FVC level ranged from 27 to 116% predicted and was within normal limits in four instances; the DLCO at first presentation ranged from 25 to 73% predicted. Furthermore, many patients with moderate or severe depression of RFT remained stable or improved during follow-up.

Table 1. - Forced vital capacity (FVC) and carbon-monoxide diffusing capacity (DLCO) level in association with normal (Group N; n=23) and abnormal (Group A; n=59) <sup>99m</sup>Tc-DTPA clearance in patients with lone cryptogenic fibrosing alveolitis (CFA) and fibrosing alveolitis associated with systemic sclerosis (SSc).

	Normal DTPA clearance	Rapid DTPA clearance	p value
<b>CFA</b>			
FVC %	91±22.3	72±25.6	p=0.1 (NS)
DLCO %	65±15.5	40±13.2	p<0.001
<b>SSc</b>			
FVC %	86±16.9	70±20.4	p<0.01
DLCO %	76±25.6	49±15.8	p<0.001

*Predictive value of serial measurement of <sup>99m</sup>Tc-DTPA clearance*

The clinical utility of serial measurement of clearance was evaluated in 54 patients (systemic sclerosis, n=42; CFA, n=12) undergoing measurement of clearance on at least two occasions. There were 33 patients in subgroup AA (persistently abnormal clearance), 8 patients in subgroup AN (abnormal clearance which reverted to normal), 12 patients in subgroup NN (persistently normal clearance) and one patient in subgroup NA (normal clearance which became abnormal). In all eight patients in subgroup AN, the clearance half-time increased by at least

10 min. The mean interval between measurements of  $^{99m}\text{Tc}$ -DTPA was  $13.1 \pm 4.2$  months (minimum interval 6 months); the interval between measurements of clearance did not differ significantly between CFA ( $13.4 \pm 4.7$  months) and systemic sclerosis ( $13.0 \pm 4.0$  months), or between subgroup AA ( $12.8 \pm 4.3$  months), subgroup AN ( $14.4 \pm 3.6$  months) and subgroup NN ( $13.0 \pm 4.1$  months). Mean follow-up for the whole population was  $33.0 \pm 7.9$  months; follow-up did not differ significantly between CFA ( $32.3 \pm 6.6$  months) and systemic sclerosis ( $33.2 \pm 8.2$  months), or between subgroup AA ( $32.0 \pm 7.2$  months), subgroup AN ( $32.9 \pm 8.0$  months) and subgroup NN ( $36.1 \pm 8.9$  months).

The relationship between changes in respiratory function tests and trends in  $^{99m}\text{Tc}$ -DTPA clearance are shown in Fig. 3. Deterioration in RFT was confined to subgroup AA; declines in RFT occurred in 14/33 patients, compared to 0/8 in subgroup AN ( $p < 0.025$ ), and 0/12 in subgroup NN ( $p < 0.01$ ). Decline in RFT within subgroup AA was more frequent in CFA (6/8) than in systemic sclerosis (8/25),  $p < 0.05$ .

Declines in RFT, from the time of the second scan until the end of follow-up, were also more frequent in subgroup AA (10/33) than in subgroup AN (0/8),  $p = 0.08$ , or subgroup NN (0/12),  $p < 0.05$ .

Significant improvements in RFT occurred more frequently in subgroup AN (6/8) than in subgroup AA (8/33),  $p < 0.02$ , or subgroup NN (2/12),  $p < 0.02$ . Improvements in RFT in subgroup AN occurred in 2/3 patients with CFA and 4/5 patients with systemic sclerosis and had largely occurred by the time of the second measurement of clearance; however in 3/8 patients, significant further improvements in RFT occurred during follow-up after the second scan.

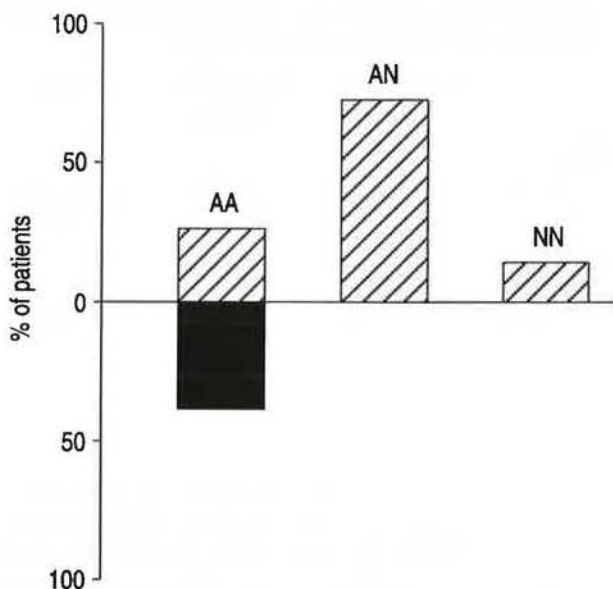


Fig. 3. - The percentage of patients with improvements (▨) or declines (■) in RFT from initial measurement of  $^{99m}\text{Tc}$ -DTPA clearance in relation to clearance trends. Improved RFT were seen most commonly in the AN group. AA: persistently rapid/abnormal clearance; AN: abnormal clearance reverts to normal; NN: persistently normal clearance.

#### The effect of treatment on $^{99m}\text{Tc}$ -DTPA clearance and RFT

The association between clearance findings and subsequent RFT trends was not attributable to differences in treatment regimens between subgroups. Decisions regarding treatment were based upon symptoms, radiological findings (including CT appearances) and physiological abnormalities and not upon clearance findings; in general, treatment was undertaken unless the patient declined therapy or the disease was limited in extent. Corticosteroid therapy and/or an immunosuppressive agent (cyclophosphamide or azathioprine) had been instituted before the first scan in 37/82 patients and was continued or started after the first scan in 64/82. The proportion of patients treated before the first scan did not differ significantly between groups A (49%) and N (52%); there was no significant difference in the proportion treated after the first scan between groups A (81%) and N (70%) or between subgroups AA (82%), AN (63%) or NN (67%). Therefore, the increased frequency of RFT deterioration in group A and in subgroup AA could not be attributed to relative lack of therapy.

Abnormal  $^{99m}\text{Tc}$ -DTPA clearance was largely unaltered by treatment. Thirty two patients with abnormal clearance at first measurement received treatment between measurements of clearance, including 17 patients who were started on standard high dose therapy. Clearance reverted to normal in only 5/32 patients (16%); in a further three patients, the half-time of clearance slowed by more than 10 min but remained abnormally rapid.

#### Discussion

The management of fibrosing alveolitis is governed by the reconciliation of two contrasting principles: the need for early intervention to prevent irreversible lung damage and fibrosis and the avoidance of significant side effects from unnecessary treatment. Ideally, patients with stable disease should be identified and observed, rather than treated intensively. In lone CFA, lung biopsy appearances provide prognostic information; a fibrotic biopsy is predictive of a poor prognosis [16, 17]. Simple noninvasive investigations such as chest radiography [7, 18] and respiratory function tests [19], do not discriminate between inflammatory and fibrotic lung disease; these procedures cannot discriminate between stable and progressive disease at first presentation. The aim of this study was to determine whether the measurement of  $^{99m}\text{Tc}$ -DTPA could make this distinction. Our findings indicate that normal  $^{99m}\text{Tc}$ -DTPA clearance is associated with subsequent disease stability whereas rapid clearance identifies a risk of deterioration, particularly if clearance has not reverted to normal at repeat measurement.

#### Mechanisms of $^{99m}\text{Tc}$ -DTPA clearance

Increased alveolar permeability has been attributed to inflammation in several interstitial lung diseases [2, 3] but this may not be the only explanation for abnormal

clearance.  $^{99m}\text{Tc}$ -DTPA clearance is abnormal in smokers [20] and rapidly reverts to normal after stopping smoking [21] but the mechanism for this is unknown. In this study, current smokers and patients who had stopped smoking less than six months before the measurement of clearance were excluded from analysis. Increased permeability might also result from stretching of epithelial junctions in the alveolar wall as a result of fibrotic traction in interstitial lung disease [22]. The more rapid clearance of  $^{99m}\text{Tc}$ -DTPA seen in the upper lobes in the upright but not the prone position in normal subjects has been attributed by some to increases in alveolar volume in the upper lobes due to gravity [23].

In two sub-groups of our patients,  $^{99m}\text{Tc}$ -DTPA abnormalities were likely to be associated with inflammation: those with clearance reverting to normal in association with improvement in RFT, and those with persistently abnormal clearance and subsequent deterioration in RFT. However, in many patients with systemic sclerosis, most of them treated, persistently abnormal clearance did not revert to normal with therapy but was not associated with RFT deterioration. It is possible that, in these patients, abnormal clearance resulted, in part, from fibrotic traction or other non-inflammatory mechanisms, producing increased alveolar epithelial permeability. These findings contrast with those in sarcoidosis, in which abnormalities of  $^{99m}\text{Tc}$ -DTPA clearance generally improve with anti-inflammatory therapy [2].

The relationship between  $^{99m}\text{Tc}$ -DTPA clearance and concurrent RFT at first measurement lends further circumstantial support to the suggestion that both alveolar inflammation and fibrotic traction might result in increased epithelial permeability. Severe depression of RFT was usually associated with abnormally rapid clearance. In some of these patients, the subsequent clinical course was indicative of inflammatory disease, but was suggestive of irreversible fibrotic disease in others.

#### *Clinical utility of measurements of $^{99m}\text{Tc}$ -DTPA clearance*

The initial measurement of clearance identified a large subgroup, approximately one third of patients, who had normal clearance and did not subsequently deteriorate, as judged by RFT; normal clearance at initial measurement was the strongest prognostic indicator in the present study. Rapid clearance at first measurement was less precise as a prognostic guide; almost half of this subgroup subsequently deteriorated whilst approximately a quarter improved.

$^{99m}\text{Tc}$ -DTPA clearance trends were analysed in order to determine whether serial measurements of clearance enhanced the predictive value of a single measurement. A second measurement of clearance a year later, when initial clearance was rapid, allowed the definition of two subgroups: patients with persistently abnormal clearance, at higher risk of decline, and patients in whom clearance reverted to normal, with a good prognosis. However, persistently abnormal clearance was not associated with subsequent decline in all patients and was thus a less powerful prognostic indicator than was normal clearance

at initial measurement. This finding suggests that no single modality should be used in isolation to stage fibrosing alveolitis. It is likely that other sensitive non-invasive modalities such as CT, which is able to discriminate between inflammatory and fibrotic lung disease [24], will enhance the predictive value of the measurement of  $^{99m}\text{Tc}$ -DTPA clearance in this subgroup of patients.

These findings have practical implications in terms of the selection of treatment and frequency of follow-up. In patients with normal clearance at first measurement, we now adopt a less aggressive therapeutic approach than formerly and have reduced the frequency of follow-up visits, usually to annual review. A second measurement of clearance, a year later, added very little information when initial clearance was normal (only one patient in the present study had developed rapid clearance on repeat testing), and therefore we have increased the interval between measurements of clearance to two years in these patients. The cost-effectiveness of this approach remains to be determined. In patients with abnormal clearance at first measurement, our general approach remains one of intervention with frequent follow-up evaluation; in this sub-group, we have continued to measure clearance at annual intervals, in order to define more precisely the group at risk of decline. The value of more than one repeat measurement of clearance is under prospective assessment.

In the present study, the severity of depression of initial RFT was an inconsistent guide to prognosis and inferior, in this regard, to measurements of clearance. In other series, the relationship between RFT and outcome has been highly variable; in studies of lone CFA [7] and systemic sclerosis [25], prognosis has been unrelated to the severity of depression of RFT at presentation. In no series has baseline RFT conferred prognostic information of the same precision as that provided by the measurement of  $^{99m}\text{Tc}$ -DTPA clearance in the present study.

#### *The relationship between $^{99m}\text{Tc}$ -DTPA clearance and treatment*

Clearance measurements were of predictive value despite the fact that not all the patients in the present study were treated. The decision to start therapy was based upon assessment of conventional indices (symptoms, chest radiography, RFT) and was not influenced by initial  $^{99m}\text{Tc}$ -DTPA findings. However there were no significant differences in the proportion of patients treated, within the subgroups analysed. Thus the predictive value of  $^{99m}\text{Tc}$ -DTPA clearance was not a spurious finding resulting from differences in therapy.

In general,  $^{99m}\text{Tc}$ -DTPA clearance remained abnormal despite treatment, a finding which mirrors the lack of response generally achieved in fibrosing alveolitis with traditional therapies [7]. However many of our patients had been referred with extensive disease; the predictive value of  $^{99m}\text{Tc}$ -DTPA clearance and its reversibility with treatment in early disease has not been addressed in this study and merits further prospective evaluation.

### Trends in CFA compared with trends in systemic sclerosis

In CFA, very rapid clearance of  $^{99m}\text{Tc}$ -DTPA was more prevalent than in systemic sclerosis, suggesting that alveolar epithelial abnormalities were more severe in the former disease. Moreover, rapid clearance was more frequently associated with subsequent deterioration of RFT in CFA. These findings are consistent with epidemiological observations; CFA has a worse prognosis than does the fibrosing alveolitis of systemic sclerosis, even when lung function parameters and demographic data are matched at first hospital presentation [26].

In conclusion, measurement of  $^{99m}\text{Tc}$ -DTPA clearance in fibrosing alveolitis discriminated between patients with stable disease and those at risk of deterioration. This finding has important clinical implications, particularly in terms of the selection and timing of follow-up and treatment.

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