shown to be very precise for determination of ^{99m}Tc-DTPA single-sample clearance. The determination was marginally more accurate if the single-sample formula was derived from the entire plasma time-activity curve than from Brøchner-Mortensen's simplified method. The single-sample formula derived for determination of ^{99m}Tc-DTPA clearance (Christensen and Groth) showed slightly, but systematically, higher values when applied on patients investigated with ^{51}Cr-EDTA, than the reference multiple-sample method. Carefulness should, therefore, be observed when deriving a single-plasma sample method from a method that is already simplified. Using the regression coefficients derived for one radiopharmaceutical on another should probably be avoided.

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Gallium-67 Scintigraphy to Predict Response to Therapy in Active Lupus Nephritis

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Gallium-67-citrate has been used to detect inflammation for decades, and ^{67}Ga uptake usually indicates an active, potentially curable lesion. In this study, we determined the value of ^{67}Ga renal scintigraphy for predicting response to therapy in patients with lupus nephritis. **Methods:** Forty-seven patients with lupus nephritis and abnormal serum creatinine or elevated 24-hr urine protein were enrolled. Delayed 48-hr ^{67}Ga imaging was performed to evaluate ^{67}Ga uptake by the kidneys. Serum creatinine and 24-hr urine protein values were obtained at the beginning of this study and after 1 yr of treatment. Serum creatinine was considered abnormal at levels greater than or equal to 1.4 mg/dl and 24-hr urine protein at levels greater than or equal to 1.0 g/day. When the value of serum creatinine or 24-hr urine protein obtained 1 yr after treatment was in the normal range or was 50% of the initial abnormal value, the patient was considered to have good response to treatment. **Results:** Gallium-67 renal scan showed good correlation with the response to therapy in patients with lupus nephritis. In the negative ^{67}Ga scan group, no significant changes in laboratory data were noted between onset of this study and after 1 yr of therapy. In the positive ^{67}Ga scan group, there were significant decreases in serum creatinine and 24-hr urine protein levels 1 yr after treatment, especially in 24-hr urine protein, with p values of 0.019 and 0.0007 respectively, by Student's t-test for dependent samples. Moreover, 11.5% of patients with a negative ^{67}Ga scan had a good response to treatment, whereas 71.4% of patients with a positive ^{67}Ga scan had a good response to treatment. **Conclusion:** We suggest that ^{67}Ga renal scan is a valuable predictor of response to therapy in patients with lupus nephritis.

Key Words: gallium-67 scan; lupus nephritis; serum creatinine; 24-hr urine protein; response to treatment

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The prognosis for patients with lupus nephritis has improved significantly in recent years, partly because of aggressive treatment with immunosuppressive drugs (*1–3*). However,

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lupus nephritis is still associated with high morbidity and death rate (*4*). It is therefore important to identify prognostic indicators to facilitate the formulation of appropriate management plans. There have been a large number of studies evaluating the prognosis of lupus nephritis over the past three decades. In general, these studies have evaluated clinical, laboratory or biopsy features at the onset of study. No research has been done to evaluate the potential of ^{67}Ga-citrate scan as a predictor of prognosis.

Gallium-67 has been used for several decades to detect inflammation. Many reports have suggested that ^{67}Ga scans help diagnose nephritis (*5–7*). Ganeval et al. (*8*) reported that intense renal ^{67}Ga uptake (equal to liver uptake) is associated with acute interstitial nephritis. Randall et al. (*9*) concluded that significant renal ^{67}Ga uptake indicates active, potentially curable lesions. The aim of this study was to determine whether an increase in ^{67}Ga uptake by the kidneys indicates active, potentially curable lesions and implies a good response to treatment in patients with lupus nephritis.

In this study, we analyzed 47 systemic lupus erythematosus (SLE) patients with lupus nephritis to determine the value of ^{67}Ga scintigraphy for predicting response to therapy. We measured response to therapy by evaluating changes in serum creatinine and 24-hr urine protein between the beginning of this study and 1 yr of treatment.

MATERIALS AND METHODS

This study included 47 patients (44 women, 3 men; aged 32.5 ± 14.4 yr.) who satisfied the diagnostic criteria for SLE established by the American Rheumatism Association (*10*) and who were clinically diagnosed with lupus nephritis. All patients had an abnormal serum creatinine or elevated 24-hr urine protein. For this study, serum creatinine was considered abnormal at levels ≥1.4 mg/dl. Twenty-four hour urine protein excretion elevation was defined as levels ≥1.0 g/day. Although the acceptable upper limit of normal for proteinuria is 0.2 g/day in healthy individuals, we chose a higher limit because patients whose nephritis is in remission may have persistent low-grade proteinuria (*11,12*).

Forty-eight hours after the injection of 5 mCi ^{67}Ga citrate, static posterior abdominal scintigrams were obtained by a large-field-of-view camera with a medium-energy, parallel-hole collimator. Three 20% windows were set at 93, 184 and 296 keV, respectively. A delayed 72-hr image was obtained when normal gallium bowel activity interfered with the interpretation. Relative uptakes by kidneys and spine were judged visually on the analog images and rated on a scale of 0 to 3+: 3+ = uptake intensity in the kidneys greater than in the spine, 2+ = intensity equal to that of the spine, 1+ = intensity less than in the spine and 0 = no renal uptake (*13, 14*). Visual grading was performed by two observers and showed excellent concordance. The test was regarded as positive when 2+ or 3+ renal uptake was demonstrated and negative at 0 to 1+ uptake (Fig. 1). Twenty-three patients had follow-up gallium studies.

Anti–double-strained DNA (anti-dsDNA) were measured in all patients. The anti-dsDNA assay used in this study was a solid-phase enzyme immunoassay method (INSCSTAR Corporation, Stillwater, MN) performed according to the manufacturer's instructions. Values were expressed as units relative to the control reference sera. The normal cutoff value was 40 U.

Forty-six patients (97.9%) received prednisone, and 29 patients (61.7%) received immunosuppressive agents (generally cyclophosphamide) in addition to prednisone. Response to treatment was assessed by comparing measurements of 24-hr urine protein and serum creatinine at the time of ^{67}Ga scan and after 1 yr of treatment. Patients were considered to have a good response to treatment when the values of serum creatinine or 24-hr urine protein obtained after 1 yr of treatment were in the normal range or were 50% of the initial abnormal value.

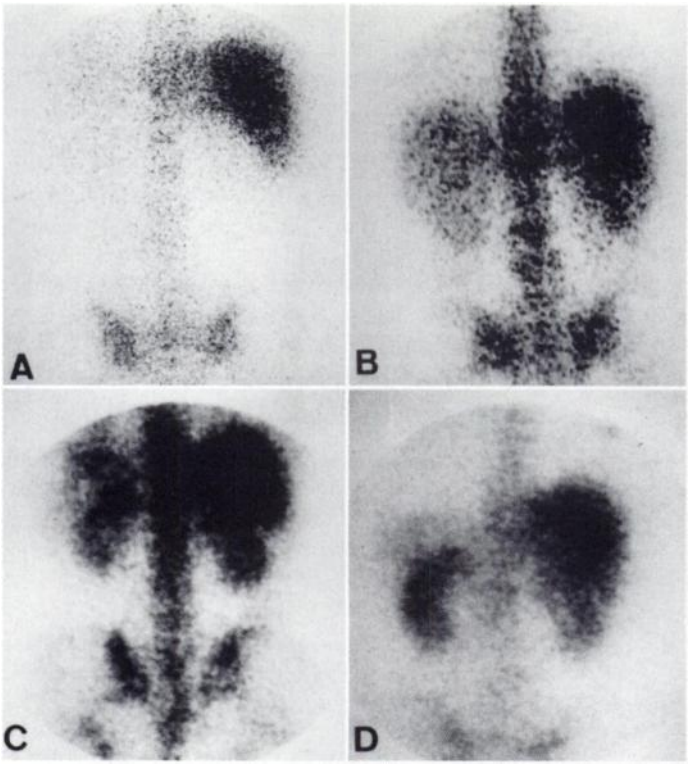

FIGURE 1. Gallium-67 scintigraphic findings in patients with lupus nephritis. (A) Grade 0: no renal uptake; (B) Grade 1: uptake intensity in kidneys less than in spine; (C) Grade 2: intensity equal to that of spine; (D) Grade 3: intensity greater than in spine.

Statistical Analysis

Data are presented as mean ± s.d. Intergroup differences for continuous variables were evaluated with the Student's t-test for dependent samples. A p value <0.05 was considered to be statistically significant. Statistical comparisons of dichotomous variables between patients with positive and negative scan results were performed using chi-square test or Fisher's exact test.

RESULTS

The detailed data of the patients with lupus nephritis are listed in Table 1. According to the results of ^{67}Ga renal scan, Table 2 shows the changes in serum creatinine and 24-hr urine protein between the beginning of this study and after 1 yr of treatment. In the negative ^{67}Ga scan group, no significant changes in these laboratory data were noted, although the initial mean values were higher than the follow-up values. In the positive ^{67}Ga scan group, serum creatinine decreased from a mean value of 2.49 mg/dl at the beginning of this study to 1.47 mg/dl after 1 yr of treatment. The difference is statistically significant with a p value of 0.019 by Student's t-test for dependent samples. In addition, 24-hr urine protein showed a more significant decrease from 3.47 g/day to 1.39 g/day ($p = 0.0007$ by Student's t-test for dependent samples).

Of the 26 patients with a negative ^{67}Ga scan, 3 (11.5%) had a good response to treatment. In contrast, of the 21 patients with a positive scan, 15 (71.4%) had a good response to treatment. The difference is very significant with a p value of 0.00003 by Fisher's exact test.

Of the 23 patients who had a follow-up scan, 18 patients had positive pretreatment gallium scans and their follow-up gallium scans correlated well with the clinical improvement. Of the 13

TABLE 1
Data of 47 Patients with Lupus Nephritis

Patient no.	Sex	Age (yr)	Ga-67 scan grade	F/U Ga-67 scan grade	Anti-dsDNA	Serum creatinine (mg/dl)		24-hour urine protein (g/day)	
						Before Tx	After Tx	Before Tx	After Tx
1	F	22	0	NA	18	9.1	7.7	0.164	0.3
2	F	24	0	NA	38	1.6	0.4	0.68	0.093
3	F	21	0	NA	616	14	9.1	1.037	0.164
4	F	38	0	NA	486	4.8	0.9	1.1	1
5	F	18	0	NA	31	1.7	0.7	1.3168	2.772
6	F	41	0	NA	412	2	1.4	1.32	1.04
7	F	36	0	NA	96	5.7	3	1.89	0.12
8	F	49	0	2	37	0.7	1.4	1.9	8.8
9	F	41	0	1	3009	3.9	2.1	2.62	6.72
10	F	21	0	NA	233	5.3	8.7	3.7	3.5
11	F	20	0	NA	76	3.4	6.1	4.4	4.3
12	F	45	1	NA	6	1.5	0.8	0.59	1.63
13	F	68	1	NA	32	2.4	2.9	0.81	0.192
14	F	52	1	NA	18	0.6	1.2	1	1.17
15	F	40	1	NA	12	1	1	1.42	2.88
16	F	65	1	NA	30	2.1	1.2	1.52	1.16
17	F	34	1	NA	1221	1	0.6	1.68	0.167
18	F	24	1	NA	556	0.7	1.75	1.8	1.75
19	F	61	1	NA	1745	5	4.2	1.83	1.33
20	F	13	1	1	917	2.7	1.1	2.41	3.65
21	F	48	1	NA	24	0.7	1.1	2.8	2.3
22	F	49	1	NA	15	0.6	0.6	2.82	1.74
23	F	21	1	NA	45	3.1	2.7	4.15	1.2
24	F	28	1	1	212	1.1	1	4.49	4.5
25	F	27	1	NA	62	1.1	1	5.5	1.25
26	F	29	1	1	385	10.3	9.9	11.8	7.54
27	F	60	2	1	17	4.2	4.4	0.552	0.418
28	F	54	2	NA	2189	1.6	1.1	0.84	0.162
29	F	27	2	1	657	4.9	1.3	1.98	0.8
30	F	28	2	0	1552	1.4	1.2	2.28	0.394
31	F	19	2	2	398	0.8	1.3	2.94	1.224
32	F	19	2	0	23	1.4	1.3	3.4	0.92
33	F	29	2	1	24	1.4	1.1	3	1.23
34	F	32	2	2	683	7.8	2.2	3.4	2.4
35	F	16	2	0	111	8.3	4.3	4	0.1071
36	F	32	2	NA	899	7.1	2	4.4	2.26
37	M	23	2	1	2178	1	1	6	1.17
38	F	15	2	NA	111	1.8	0.6	6.588	2.2
39	F	19	2	2	9	1.1	1.2	1.2	3.2
40	M	23	2	2	34	1.2	1.4	1.3	4.325
41	F	54	3	1	68	0.7	0.8	4.12	0.34
42	F	28	3	1	254	1.2	0.8	6.396	0.46
43	F	35	3	2	412	1.9	0.9	1.314	1.5
44	M	15	3	1	92	1.4	1	2.56	1.1
45	F	26	3	1	357	1.3	1.1	4.09	1.91
46	F	19	3	1	1098	0.9	1.2	4.68	1.62
47	F	22	3	1	344	1	0.8	8.3	1.2

F/U = follow-up; anti-dsDNA = anti-double-strained deoxyribonucleic acid; Tx = treatment.

patients whose gallium results went from positive to negative (Fig. 2), 12 showed a good response to treatment on the basis of the laboratory data. In contrast, of the 5 patients whose gallium results remained positive after treatment, only 1 had a good response to treatment. Of the 26 patients with a negative pretreatment gallium scan, only 5 had follow-up gallium studies. It was difficult to draw a conclusion based on the limited data.

The correlation between gallium grading and serum level of anti-dsDNA was poor (r = 0.1, Spearman's nonparametric correlation). Of the 26 patients with negative gallium scan results, 15 had an elevated serum anti-dsDNA level. Of the 21 patients with positive gallium scan results, 16 had an elevated serum anti-dsDNA level. There was no statistical significance at p value of 0.18 using the chi-square test.

DISCUSSION

Gallium-67 has been used in the study of renal inflammatory disorders for many years. According to Linton et al. (*6*), ^{67}Ga scintigraphy is an excellent screening test for the presence of acute interstitial nephritis. Pagniez et al. (*15*) concluded that significant renal ^{67}Ga uptake indicates active, potentially curable lesions. However, only two reports regarding the use of ^{67}Ga in lupus nephritis have been published. Wood et al. (*16*)

TABLE 2
Changes in Serum Creatinine and 24-Hour Urine Protein Between Beginning of Study and After 1 Year of Treatment

	Negative Ga-67 scan (n = 26)				Positive Ga-67 scan (n = 21)			
	Serum creatinine (mg/dl)		24-hour urine protein (g/day)		Serum creatinine (mg/dl)		24-hour urine protein (g/day)	
	Before Tx	After Tx	Before Tx	After Tx	Before Tx	After Tx	Before Tx	After Tx
Mean	3.31	2.79	2.49	2.35	2.49	1.47	3.47	1.39
1 s.d.	3.34	2.93	2.33	2.35	2.37	0.99	2.08	1.05
p value*	0.134		0.762		0.019		0.0007	

*By Student's t-test for dependent samples.
Tx = treatment.

described a positive renal scan in a patient with SLE. Defining active renal disease by the presence of hematuria, pyuria, proteinuria, a rising serum creatinine level or a biopsy specimen, Bakir et al. (*17*) performed ^{67}Ga scans in 43 patients with SLE and reported that 89% of patients with active renal disease had positive ^{67}Ga findings, whereas only 17% of patients with inactive renal disease had positive ^{67}Ga findings. The relationship between ^{67}Ga renal scan and response to treatment has not been investigated.

Our data showed that a positive ^{67}Ga scan in patients with lupus nephritis indicates a good response to treatment. In the positive ^{67}Ga renal scan group, 71.4% of patients had a good response to treatment. In contrast, more than 88% of patients had a poor response to treatment in the negative ^{67}Ga renal scan group. In addition, a follow-up gallium scan seemed to be useful in evaluating the response to treatment in patients with active lupus nephritis. Of the 5 patients whose gallium results remained positive in the follow-up studies, 4 did not have a good response to treatment. On the basis of the limited data, the combination of an initial and a follow-up gallium scan may help increase the value of gallium scanning in predicting response to treatment. These findings suggest that an increase in ^{67}Ga uptake by the kidneys indicates active, curable lesions. The results are also compatible with our previous report (*13*), in which ^{67}Ga renal scanning correlated well with the activity index but not the chronicity index of renal biopsy. These data suggest that ^{67}Ga uptake is associated with an acute lesion rather than a chronic lesion. However, 3 patients with negative gallium results had good responses to treatment in this study. Similar results were reported by Cruzado et al. (*14*). In their study, pretreatment ^{67}Ga scans of the kidneys were negative in two patients with sarcoidosis who had interstitial nephritis.

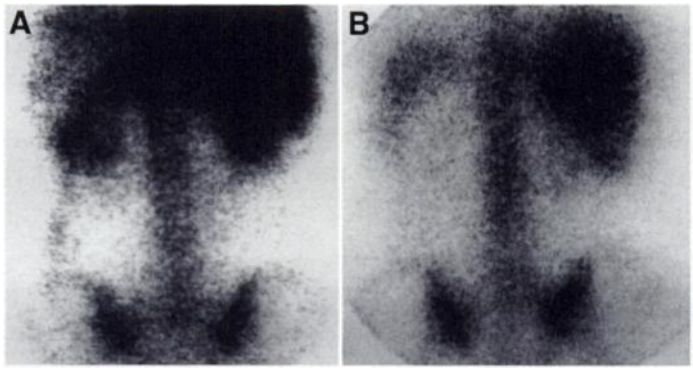

FIGURE 2. Nineteen-yr-old woman with active lupus nephritis. (A) Posterior ^{67}Ga renal scan shows increased gallium uptake in both kidneys with intensity equal to spine uptake (Grade 2). (B) After treatment, no abnormal gallium uptake is noted in either kidney (Grade 0).

However, the response to steroid treatment was excellent in both patients. They concluded that the absence of ^{67}Ga renal uptake does not guarantee that the disease is not active in the kidneys.

Various mechanisms have been proposed for the accumulation of ^{67}Ga in inflammatory lesions, including transportation by polymorphonuclear leukocytes, binding to proteins such as transferrin and lactoferrin, uptake by polymorphs, leakage of ^{67}Ga through capillaries with increased permeability and uptake by lysosomes in mononuclear phagocytes and direct binding to the lymphocyte membrane (*16,18,19*). However, the exact mechanism is still unknown. It is likely that one or more of the these mechanisms resulted in the observed ^{67}Ga uptake by the kidneys.

In this study, we noticed that ^{67}Ga renal scanning predicted the response of 24-hr urine protein better than did serum creatinine levels. This finding is reasonable because serum creatinine levels often remain normal in patients with significant renal damage because of compensatory mechanisms, and abnormal serum creatinine levels are related to both acute reversible lesions and chronic irreversible lesions. Conversely, proteinuria may be present in patients with minimal glomerular injury and represents acute, reversible lesions that usually respond to treatment better than do chronic lesions.

Several studies have found the response to treatment to be a valuable predictor of long-term outcome (*20–23*). Because the results of ^{67}Ga renal scanning showed good correlation with the response to treatment, ^{67}Ga renal scanning also may be able to predict long-term outcome. To elucidate this point, further evaluation is needed.

The presence of anti-dsDNA has been considered to be a useful predictor of disease activity in lupus nephritis (*24*). However, in this study, there was no significant relationship between serum anti-dsDNA and gallium scan, and anti-dsDNA was not good at predicting response to treatment. Two possible reasons for the lack of significant correlation between these two examinations may be: (a) the type of assay used [A Farr assay method has been reported more specific than an enzyme immunoassay method in association with active lupus nephritis (*25,26*).], and (b) discrepancy between different races. Anti-dsDNA may not be a good test to evaluate lupus nephritis in a Chinese population.

According to these data, ^{67}Ga renal scan is valuable as a predictor of the response to therapy in patients with lupus nephritis, especially when the laboratory data, such as serum creatinine or 24-hr urine protein, are abnormal. A positive ^{67}Ga scan implies a better chance for good response to therapy.

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Scintigraphic Localization of Lymphatic Leakage Site After Oral Administration of Iodine-123-IPPA

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Chylothorax can occur secondary to traumatic lesions of the thoracic duct caused by chest injuries, surgical procedures involving the pleural space, neoplasms or malformations of the lymphatics. **Methods:** Lymphatic leakage sites were localized by scintigraphy after oral administration of the ^{123}I-labeled long-chain fatty acid derivative iodophenyl pentadecanoic acid (IPPA). We report on three patients with different lymphatic leakage sites and on one normal control subject. **Results:** IPPA scintigraphy localized the lymphatic leakage site correctly in all three patients. In two of them, the method even guided the successful surgical treatment of the leakage. **Conclusion:** This approach is suitable for detecting lymphatic leakages of intestinal origin.

Key Words: thoracic duct; lymphatic leakage; iodine-123-iodophenyl pentadecanoic acid

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The thoracic duct originates from the cisterna chyli, enters the chest through the aortic hiatus, curves around the right side of the aorta, continues on the anterior surface of the vertebral column and crosses the posterior surface of the aorta to the left at the level of the fifth thoracic vertebra (T5) finally merging into the venous system at the left jugulosubclavian junction (Fig. 1). This anatomy explains how injuries below the level of T5–6 usually cause a right-sided chylothorax, whereas injuries above this level result in a left-sided effusion. Indeed, the anatomical location of the thoracic duct tends to vary greatly from individual to individual.

Depending on the frequency of food intake and fat content, leakage can have a flow rate of 1.5 ml/kg of body weight per hour. Clinically, leakage involves an accumulation of chyle in the pleural space associated with compression of the ipsilateral lung and mediastinum and can lead to dyspnea, fatigue and discomfort. Biochemically, up to 2500 ml of fat, protein, fat-soluble vitamins and antibodies can be lost over a period of 24 hr.

Before the first successful surgical closure of the leakage (*1*), the mortality of chylothorax ranged between 15% and 50%. Currently, mortality is less than 10% due to multimodal surgical approaches. Conservative therapy consists of thoracostomy including placement of tube drainage and correction of both fluid losses and electrolyte imbalance.

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