CHEST

Original Research

DIFFUSE LUNG DISEASE

Accuracy of Individual Variables in the Monitoring of Long-term Change in Pulmonary Sarcoidosis as Judged by Serial High-Resolution CT Scan Data

Christopher J. Zappala, MD; Sujal R. Desai, MD; Susan J. Copley, MD; Paolo Spagnolo, PhD; Derek Cramer, MIScT; Dushendree Sen; Salma M. Alam, MBBS; Roland M. du Bois, MD; David M. Hansell, MD; and Athol U. Wells, MD

Background: **In pulmonary sarcoidosis, the optimal means of quantifying change is uncertain. The comparative usefulness of simple lung function trends and chest radiography remains unclear. We aimed to explore and contrast the disease-monitoring strategies of serial pulmonary function tests (PFTs) and chest radiography compared against morphologic change on high-resolution CT (HRCT) scan.**

Methods: **Seventy-three patients with sarcoidosis were identified who had two HRCT scans with concurrent chest radiography and PFTs. Chest radiography and HRCT scans were assessed by two radiologists for change in disease extent. Concordance between the scoring systems, as well as agreement between PFT trends (% change from baseline in FEV, FVC, and diffusing capacity of the lung for carbon monoxide [DLCO]), chest radiography, and chest HRCT scan change, were examined using the weighted κ coefficient of variation (Kw).**

Results: **There was fair agreement between change in extent of disease on chest radiograph and significant PFT trends (Kw = 0.35, $P < .001$) and moderate agreement between change in extent of disease on serial HRCT scan and significant PFT trends (Kw = 0.64, $P < .0001$). The integration of DLCO trends did not improve concordance between change on HRCT scan and PFT change. Change in gas transfer coefficient (ie, DLCO/alveolar volume) displayed no overall linkage with change in disease extent on chest radiograph (Kw = 0.07, $P = .27$) and only poor agreement with change in disease extent on HRCT scan (Kw = 0.17, $P = .07$).**

Conclusions: **Significant PFT trends correlate better with morphologic change as defined by serial HRCT scan than extent of disease on radiograph. Isolated change in gas transfer coefficient is more frequently discordant with change in disease extent on chest radiograph and HRCT scan and may suggest a pulmonary vascular component.** ***CHEST 2014; 145(1):101–107***

Abbreviations: DLCO = diffusing capacity of the lung for carbon monoxide; HRCT = high-resolution CT; KCO = gas transfer coefficient; Kw = weighted κ coefficient of variation; PFT = pulmonary function test

The most recent international consensus document on the management of sarcoidosis states that serial chest radiography and spirometry should be used to identify changes in disease severity.[1] We showed that there was discordance between change in extent and change in stage on chest radiography in sarcoidosis.[2] Change in disease extent, scored using a simple, semiquantitative scale, is more sensitive than change in stage, has more functional significance, and is, therefore, the preferable means of assessing the evolution of pulmonary sarcoidosis. However, the comparative usefulness of simple lung function trends and chest radiography remains unclear.

The optimal means to measure disease behavior in sarcoidosis remains uncertain. The usefulness of serial HRCT scans in sarcoidosis as a routine monitoring strategy is questionable and not recommended in current guidelines.[1,3] However, based on the advantages of simple side-by-side comparison, demonstrated in serial chest radiographic studies,[4-7] it is possible to construct a similar HRCT scan system in which the simple designation of definite morphologic change

can be determined and then used as a comparator for serial change in PFTs and chest radiograph appearance. In this way, correlations between alternative monitoring strategies, using varying combinations of pulmonary function tests (PFTs) and chest radiography, can be compared. This study explores monitoring strategies in sarcoidosis by comparing significant PFT trends and chest radiographic appearance with fine morphologic change as defined by HRCT scanning.

Materials and Methods

We reviewed data from 73 patients collected between January 1, 1993, and December 31, 2005, who met current clinical and histopathologic diagnostic criteria for pulmonary sarcoidosis.[1] All patients had a baseline HRCT scan of the chest and a follow-up scan. Clinical data were extracted from case records (Table 1). As the aim of the study was to reconcile change in chest HRCT scan with changes in PFT indices and/or chest radiography, treatment effects were not specifically evaluated.

The follow-up HRCT scan was broadly requested when clinically indicated to investigate nonspecific, new/persistent symptoms (n = 21) or ambiguity regarding change in disease severity, generally reflecting discrepancies between clinical data (n = 52). The median time interval between scans was 3.2 years (range, 0.4-13.4 years). The specific indications for the repeat HRCT scan was to investigate (1) clinical evidence of recent decline over weeks to months (suspected disease progression or infection) (n = 45), (2) clinical evidence suggesting insidious disease progression over years (n = 20), and (3) clinical evidence suggesting disease regression over months to years (n = 8).

HRCT scan appearances were indicative of fibrotic disease in 45 cases. In the remaining 28 cases, significant reversible disease could not be excluded from HRCT image findings. In this subgroup, all patients had a time interval of < 1 month between chest radiograph and PFTs (median, 18.5 days and 0 days at baseline and follow-up, respectively) with no major treatment changes during this interval.

Relapsed disease was confirmed in 66 cases, acute infection confirmed in 22 cases, simple restaging of disease undertaken in 11 cases, and pretransplant assessment performed in two cases. HRCT scan appearances were indicative of fibrotic disease in 45 cases. In the remaining 28 cases, significant reversible disease could not be excluded from HRCT scan findings. In this subgroup, all patients had a time interval of < 1 month between chest radiograph and PFTs (median, 18.5 days and 0 days at baseline and follow-up, respectively) with no major treatment changes during this interval.

Analyzed lung function measurements consisted of FVC and FEV_1 (PKM spirometer; P. K. Morgan; or the Jaeger Compact system; CareFusion Corporation) and Dlco and gas transfer coefficient (Kco) (using a single-breath technique or a rebreathing technique with adjustment to single-breath values on a P. K. Morgan respirometer). Results were expressed as percentages of predicted values.[8]

Paired chest radiographs were assessed independently by two radiologists. To simulate radiographic interpretation in routine practice, blinding to chronological order of the chest radiograph was not undertaken. All available chest radiographs were assessed for stage of disease as per the Scadding system.[9] Change in overall radiographic severity was assessed using a simple three-point scoring system: 1 = improvement, 2 = no change, 3 = decline. Different observations were resolved by consensus.

Paired HRCT scans were assessed independently by the same two radiologists at a different point in time from assessment of chest radiographs. Scorers were blinded to the chronologic order of HRCT scans, randomized by coin toss. HRCT scans were assessed side by side for an overall change in disease extent. The scans were divided into upper, middle, and lower zones on each side, using the carina and pulmonary venous confluence as anatomic landmarks, with an assessment made in each zone of change in disease extent, using the same three-point scoring system as for chest radiography. A discordant reduction in disease extent in one zone but increased disease extent in another would equate to no overall change in scan appearance. Therefore, a change in scan appearance required a net overall impression of change incorporating all zones, as reflected in routine clinical practice. In primary analyses, change in HRCT scan was defined as change in a single HRCT scan zone. For selected subanalyses, alternative thresholds for HRCT scan change were defined (change in two zones and, separately, change in three zones).

Data Analysis

Serial trends, expressed as percentages of baseline values, were defined as significant using current American Thoracic Society criteria (FVC > 10%, Dlco > 15%, Kco > 15%, FEV_1 > 10%).[10] Significant changes in PFTs were synthesized into a three-point scale: 1 = improvement, 2 = no change, 3 = decline.

Table 1—*Baseline Patient Characteristics*

Characteristic	Value
Age, y	46.65 ± 12.2
Sex, male (female)	33 (40)
Median time between CT scans, y	3.2 (0.4-13.4)
FEV_1	74.15 ± 23.9
FVC	81.17 ± 23.8
Dlco	58.96 ± 17.5
Kco	82.34 ± 15.8
Baseline chest radiography stage, No. (%)	
0	10 (14)
I	9 (12)
II	24 (33)
III	10 (14)
IV	20 (27)

Dlco = diffusing capacity of the lung for carbon monoxide; Kco = gas transfer coefficient.

Manuscript received December 23, 2012; revision accepted July 17, 2013.
Affiliations: From the Department of Respiratory Medicine (Dr Zappala), Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia; the Interstitial Lung Disease Unit (Drs Zappala, Spagnolo, Alam, du Bois, and Wells and Ms Sen), Department of Imaging (Dr Hansell), and Department of Lung Physiology (Mr Cramer and Ms Sen), Royal Brompton Hospital and National Heart and Lung Institute London, England; the Department of Medicine (Dr Zappala), University of Melbourne, Melbourne, VIC, Australia; The Department of Radiology (Dr Desai), King's College Hospital, London, England; and the Department of Radiology (Dr Copley), Hammersmith Hospital, London, England.
Funding/Support: The authors have reported to *CHEST* that no funding was received for this study.
Correspondence to: Athol U. Wells, MD, Interstitial Lung Disease Unit, Royal Brompton Hospital and NHLI, Imperial College, Emmanuel Kaye Bldg, 1B Manresa Rd, London, SW3 6LR, England; e-mail: athol.wells@rbht.nhs.uk

DOI: 10.1378/chest.12-2479