Original article

Interstitial lung disease related to rheumatoid arthritis: Evolution after treatment

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ARTICLE INFO

Article history:
Received 26 August 2011
Accepted 8 December 2011
Available online 15 February 2012

Keywords:
Rheumatoid arthritis
Interstitial lung disease
Methotrexate
Pulmonary function tests

ABSTRACT

Objective: To describe the evolution of lung function in a cohort of rheumatoid arthritis (RA) patients with interstitial lung disease (ILD) treated according to the medical judgment of attending physicians.

Methods: Retrospective cohort of RA patients with ILD, defined by a restrictive pattern in lung function tests and evidence of ILD in high resolution computed tomography (HRCT). Patients had an assessment of lung function including spirometry, diffusing capacity for carbon monoxide (DLCO), and HRCT. At a minimum of 4 months of follow up, a second assessment of lung function was done. All patients received a high dose of prednisone (1 mg/kg/day) scheme for 6 weeks with a reduction scheme ending with a dose of 10 mg/day of prednisone at about 6–8 months of follow up. Methotrexate was used in 18/40 (45%) patients and leflunomide or azathioprine or both were indicated in 22/40 (55%).

Results: Forty patients were identified. An indeterminate pattern with diffuse ground glass and reticulation images (50%) was the most prevalent pattern on HRCT scans. At a minimum of 4 months of follow up, an improvement in basal FVC values was observed (median [IQR]) 1.67 Lts. (0.99–1.91) vs 1.66 Lts. (1.37–2.1), P<0.004. Patients with lower Kazerooni scores for fibrosis (<0.47) had a better improvement in the FVC values.

Conclusions: Patients with RA and ILD may have an improvement in the FVC after a treatment with high doses of corticosteroids and disease modifying antirheumatic drugs (DMARDs).

La enfermedad pulmonar intersticial relacionada con la artritis reumatoide: evolución después del tratamiento

RESUMEN

Objetivo: Describir la evolución de la función pulmonar en una cohorte de pacientes con enfermedad pulmonar intersticial asociada a la artritis reumatoide (EPI-AR), tratados de acuerdo al juicio de sus médicos tratantes.

Métodos: Estudio de cohorte retrospectivo de pacientes con EPI-AR, demostrada con un patrón restrictivo en las pruebas de función pulmonar, y de enfermedad pulmonar intersticial en las tomografías de alta resolución (HRCT). Los pacientes tuvieron una evaluación basal de la función pulmonar que incluyó espirometría, DLCO y HRCT. En un mínimo de 4 meses, una segunda evaluación de la función pulmonar fue realizada. Todos los pacientes recibieron una dosis alta de prednisona (1 mg/kg/día) por 6 semanas con un esquema de reducción, con una dosis de prednisona de 10 mg/día a los 6 y 8 meses de seguimiento. Se prescribió metotrexate en 18/40 (45%) pacientes, leflunomida o azatioprina, o ambas en 22/40 (55%) pacientes.

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### Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease that can cause interstitial lung and airway disease.\(^1\) Lung involvement confers a poor prognosis and it is an important cause of death in RA patients.\(^2,3\) A cohort study described that the cumulative incidence for interstitial lung disease (ILD) in RA is 7.8%.\(^4\) Nowadays, there is no consensus of how patients should be treated. It has been proposed that the American Thoracic Society/European Respiratory Society (ATS/ERS) classification for idiopathic interstitial pneumonias should be used to classify RA patients with interstitial lung disease, and there is evidence that the tomographic pattern of lung disease may be an important prognostic factor.\(^5-8\) This study was done with the aim to describe the evolution of lung function at the 6 months of follow up after baseline in a cohort of RA patients with ILD, treated according to the medical judgment of the attending physician and to describe if there is a difference in the response to treatment according to the tomography findings.

### Methods

This is a retrospective cohort of RA patients according to the ACR/87 classification criteria,\(^9\) all with ILD defined by a restrictive pattern in lung function tests (TLC <80%, normal FEV1/FVC and FVC <80%) and with evidence of ILD in high resolution computed tomography (HRCT) and a low diffusing capacity for carbon monoxide (DLCO). Patients were evaluated and treated in the interstitial lung diseases unit at the Instituto Nacional de Enfermedades Respiratorias, a national referral center for respiratory diseases. Attending physicians (pulmonologists and rheumatologists) have experience in the medical assessment of ILD. At baseline patients have an evaluation of lung function including spirometry, DLCO, and HRCT. Then, at a minimum of 4 months of follow up, a second assessment of lung function was done.

A complete description of baseline HRCT findings was done. HRCT findings were classified according the ATS/ERS criteria. The HRCT reader was blinded to clinical data. A Kazerooni scale for fibrosis and inflammation was also calculated.\(^10\) Our reader has a high intraobserver concordance in the Kazerooni score, with an intraclass correlation coefficient of 0.90 (95% CI: 0.84–0.94). HRCT was performed with 1.0 or 1.5 mm thick axial section taken at 1 cm intervals throughout the entire thorax and were reconstructed using a high-spatial frequency algorithm. Between 20 and 25 CT scans images were acquired in each patient. The study was approved by the Institutional Review Board of our institute. As this is a retrospective study, no written informed consent from patients was taken.

### Statistical analysis

Pulmonary function tests values were compared at a 6-month follow up with basal values with the Wilcoxon signed-rank test or the t-test for paired data. \(\alpha\) was set at 5%, all analyses are two sided.

### Results

Forty patients with ILD related to RA were identified, 90% were female with a mean age of 58.5 ± 9.86 years. Respiratory symptoms to diagnosis had a median of 13 months. The majority of patients had a long duration of RA disease, with a median of articular symptoms of 64 months (IQR 12–150); only 40.6% of patients used disease modifying antirheumatic drugs (DMARDs) before the diagnosis of ILD related to RA. The rest of demographics and the clinical characteristics of the patients are presented in Table 1.

Medical treatment was decided by the attending physician. A myriad of treatments was used, nevertheless all patients received a high dose of prednisone (1 mg/kg/day) scheme for 6 weeks with a reduction scheme to end with a dose of 10 mg/day of prednisone at about the 6–8 months of follow up. DMARDs used are described in Table 1. Methotrexate was used in 18/40 (45%) patients and leflunomide or azathioprine or both were indicated in 22/40 (55%). At a minimum of 4 months of follow up (median of 10.5 months of follow up, IQR: 6–18 months of follow up) an improvement in basal FVC values was observed (median [IQR] 1.47 Lts. (0.99–1.91) vs. 1.66 Lts. (1.37–2.11), \(P<0.004\) (Table 2). No differences were found between the DMARDS used. Patients had a median of 22.5 months of follow up after the basal evaluation. Four patients died, one of right heart failure, two of acute exacerbations and one died in an outpatient setting, possibly of respiratory failure. The median of survival

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients included in the study.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>(n = 40)</td>
</tr>
<tr>
<td>Female sex</td>
<td>36 (90)</td>
</tr>
<tr>
<td>Age (year old, mean ± SD)</td>
<td>58.5 ± 9.86</td>
</tr>
<tr>
<td>Years of formal education (median, IQR)</td>
<td>3 (0–9)</td>
</tr>
<tr>
<td>Duration of respiratory symptoms at baseline in months (median, IQR)</td>
<td>14 (3–36)</td>
</tr>
<tr>
<td>Rheumatoid arthritis symptoms at baseline in months (median, IQR)</td>
<td>64 (12–150)</td>
</tr>
<tr>
<td>Previous use of DMARDS</td>
<td>13/32 (40.6%)</td>
</tr>
<tr>
<td>Previous use of methotrexate</td>
<td>11/32 (34.4%)</td>
</tr>
<tr>
<td>Previous use of leflunomide</td>
<td>3/32 (9.4%)</td>
</tr>
<tr>
<td>Patients treated with methotrexate in our institute</td>
<td>18/40 (45%)</td>
</tr>
<tr>
<td>Methotrexate + leflunomide</td>
<td>3/18</td>
</tr>
<tr>
<td>Methotrexate + azathioprine</td>
<td>6/18</td>
</tr>
<tr>
<td>Patients treated with azathioprine or leflunomide without methotrexate</td>
<td>22/40 (55%)</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>12/22</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>10/22</td>
</tr>
<tr>
<td>Azathioprine + leflunomide</td>
<td>6/22</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>First evaluation (n = 40)</th>
<th>Six months follow up (n = 40)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (l)</td>
<td>1.47 (0.99–1.91)</td>
<td>1.66 (1.37–2.1)</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>FVC (%)</td>
<td>0.62 (0.42–0.77)</td>
<td>0.73 (0.56–0.91)</td>
<td>&lt;0.003</td>
</tr>
</tbody>
</table>

\(^a\) Median (IQR).
was 64 months. No differences were found between DMARDs and survival.

High resolution CT results

We had the initial HRCT of 33 patients, of these, 4 (12%) had a usual interstitial pneumonia (UIP) pattern, 12 (38%) had nonspecific interstitial pneumonia (NSIP) pattern and 17 (50%) had an indeterminate pattern with diffuse ground glass and reticulation images (Figs. 1 and 2). The median of the Kazerooni fibrosis scales was 0.47 and the median of the Kazerooni ground glass scale score was 2.33 (Table 3). We compared the response in the FVC at 6 months of follow up between patients with a value <0.47 of the fibrosis Kazerooni scale and those who had higher values. Those with lower Kazerooni scores (<0.47) were the ones who had a significant improvement in the FVC values (Table 4).

Discussion

The results in this study show that patients with RA and ILD may have an improvement in the FVC after a treatment with high doses of corticosteroids and DMARDs. This improvement is related to the fibrosis grade present at the beginning of the medical treatment, because patients with lower Kazerooni fibrosis scores were the ones who had a better improvement in the FVC values.

The general characteristics of the patients deserve some commentaries. First, although patients had a median duration of RA symptoms of 64 months, only 40% of the patients had a history of previous use of DMARDs. So, the majority of EPI-RA patients described in this cohort had not been treated according to current guidelines. Although male sex has been described as a risk factor...
Table 4
Comparison of FVC values at baseline and at a minimum of 6 months of follow up according to the median of the Kazerooni fibrosis scale score of the sample, patients with less of 0.47 had a statistically significant improvement of the FVC basal values.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Forced vital capacity (% of predicted)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At baseline</td>
<td></td>
</tr>
<tr>
<td>Kazerooni fibrosis score &lt;0.47, n = 15</td>
<td>0.65(0.42–0.80)</td>
<td></td>
</tr>
<tr>
<td>Kazerooni fibrosis score ≥0.47, n = 18</td>
<td>0.63(0.42–0.74)</td>
<td></td>
</tr>
</tbody>
</table>

*The comparison of the FVC (% of predicted) at a minimum of 6 months of follow up between patients with Kazerooni scale score values <0.47 vs ≥0.47 was of P < 0.005.

References