Hepatic Steatosis and Disease Activity in Subjects with Psoriatic Arthritis Receiving Tumor Necrosis Factor-α Blockers

MATTEO NICOLA DARIO Di MINNO, SALVATORE IERVOLINO, ROSARIO PELUSO, ANNA RUSSOLILLO, ROBERTA LUPOLI, RAFFAELE SCARPA, GIOVANNI DI MINNO, GIOVANNI TARANTINO, and the CaRRDS Study Group

ABSTRACT. Objective. Little is known about tumor necrosis factor-α (TNF-α) blockers, disease activity, and liver steatosis (hepatic steatosis; HS) in subjects with psoriatic arthritis (PsA). We prospectively evaluated changes in HS during treatment with TNF-α blockers.

Methods. In 48 patients with PsA who had evidence of HS before the beginning of TNF-α blocker treatment, an ultrasound followup examination was performed after a 12-month treatment period with TNF-α blockers. All subjects were stratified according to minimal disease activity (MDA) or not (n-MDA), during treatment with TNF-α blockers. Changes in grade of HS were evaluated in parallel in 42 controls with HS and without PsA.

Results. At baseline, no significant difference in HS score was found between PsA subjects and controls (HS scores 1.46 ± 0.65 vs 1.62 ± 0.66, respectively; p = 0.249). At 12-month followup, a worsening HS score was found in 20 (41.7%) patients with PsA and in 6 (14.3%) controls (p = 0.005). Overall, the grade of HS worsening was higher in patients with PsA (0.37 ± 0.70) than in controls (0.09 ± 0.43; p = 0.028). A significantly lower prevalence of worsening HS was found among patients with PsA with MDA, compared with n-MDA subjects (16.7% vs 66.7%, respectively; p = 0.001). Laboratory measures of liver function behaved similarly. The risk of worsening HS in patients with PsA who had MDA was similar to that in controls (HR 1.20, 95% CI 0.34–4.33, p = 0.77), and higher in patients who did not have MDA (HR 4.46, 95% CI 1.73–11.47, p = 0.001, regression analysis).

Conclusion. Compared with patients with MDA, those with active disease after 12-month treatment with TNF-α blockers exhibited significantly higher incidence of worsening liver steatosis.

Key Indexing Terms: LIVER STEATOSIS MINIMAL DISEASE ACTIVITY INFLAMMATION TUMOR NECROSIS FACTOR-α
has been reported in patients with PsA. By inhibiting proinflammatory cytokines, TNF-α blockers reduce the prevalence of MetS, liver fibrosis, and steatohepatitis. Little is known about TNF-α blockers, disease activity, and the severity of liver steatosis. We prospectively evaluated changes in the ultrasound (US) grade of HS in patients with PsA receiving 12 months' treatment with TNF-α blockers.

MATERIALS AND METHODS

In a 24-month period (January 2009-January 2011), 148 consecutive patients with a diagnosis of PsA (CASPAR criteria) referred to the Regional Centre for Biologic Treatment of Rheumatic Diseases underwent an abdominal US evaluation for the presence of HS. All were nonresponders to traditional treatments and eligible for therapy with TNF-α blockers. Exclusion criteria for enrollment were lack of informed consent, previous treatment with TNF-α blockers, withdrawal of anti-TNF-α treatment prior to 12 months of followup, history of chronic infectious disease (including hepatitis B and C), malignancy, hematologic diseases and autoimmune diseases other than PsA, unstable medical conditions, and alcohol consumption (according to Diagnostic and Statistical Manual of Mental Disorders-IV criteria and other laboratory tests).

A US diagnostic system (Logiq P5, General Electric, Milan, Italy) with a 3.5-MHz convex probe was used for this study. US determinations were carried out separately by 2 expert investigators (GT and AR), specialists in internal medicine, from the Hepatology Unit of the Department of Clinical and Experimental Medicine, Federico II University. Each was unaware of the diagnostic conclusions of the other investigator. Interinvestigator variability, as evaluated in 10 US determinations in as many PsA subjects and in 10 controls, showed an overall r value of 0.95 (p < 0.001). According to previously validated scores, comparison with the kidney cortex was used to establish an US scale of liver echogenicity: Grade 0 (absent) = isoechogenicity; Grade 1 (mild) = diffuse and homogeneous hypechoegenicity; Grade 2 (moderate) = attenuation of the ultrasound signal; and Grade 3 (severe) = lack of diaphragm profile visualization.

At baseline (T0), 51/148 patients with PsA who had US evidence of HS (scale ≥ 1) and were enrolled in the study as the case group. In parallel, 51 consecutive HS subjects without PsA, who had been referred during the same period to the metabolic outpatients clinic of our hospital and were examined by the same 2 US investigators, and who were matched with our PsA patients for demographic and clinical features, were chosen as an appropriate control group. At T1 (12 months later ± 15 days), a second abdominal US assessment was performed in cases and controls by the same 2 investigators, who were blinded to the rheumatologic evaluation to that timepoint. US worsening from baseline was defined as at least 1 grade of progression of the HS. Information on age, sex, disease duration, vascular risk factors, and previous or current treatments was collected for cases and controls as described at T0 and at T1. At both T0 and T1, all PsA subjects also underwent a complete clinical rheumatologic and laboratory evaluation including tender joint count (TJC), swollen joint count (SJC), tender enthesal count, Psoriasis Area and Severity Index (PASI), Health Assessment Questionnaire (HAQ), visual analog scale (VAS) for pain, patient global disease activity VAS score, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum transaminases. Subjects were classified as having achieved minimal disease activity (MDA) when fulfilling 5 of the following 7 outcome measures at T1: TJC ≤ 1, SJC ≤ 1, PASI ≤ 1 or body surface area ≤ 3, VAS for pain ≤ 15, patient global disease activity VAS score ≤ 20, HAQ ≤ 0.5, and tender enthesal points ≤ 113. Otherwise they were considered as not having MDA.

Statistical analysis. Statistical analysis was performed with SPSS V16 (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as means ± SD, categorical variables as percentages. To compare continuous variables, an independent sample T test was used for paired samples was used as a nonparametric equivalent of the paired samples t test used for continuous variables, to test HS score changes during treatment. Abdominal obesity, hypertriglyceridemia, hypercholesterolemia, hypertension, impaired fasting glucose, smoking status, and MetS were analyzed as dichotomous (1/0) categories. The chi-square test was used to analyze categorical data. When the minimum expected value was < 5, Fisher's exact test was used. To evaluate the risk of progression of HS, a logistic regression model was adopted (stepwise method), with worsening HS being the dependent variable, and these independent variables: ESR, CRP, sex, age, disease activity, disease duration, concomitant treatment with methotrexate (MTX), treatment with statins and/or omega-3 fatty acids, baseline HS grade, smoking habit, diabetes, obesity, hypercholesterolemia, hypertriglyceridemia, and hypertension. Multicollinearity effect in multi-variable regression models was excluded by a stepwise approach with variable included for p < 0.05 and excluded for p > 0.1. A tolerance test was used to exclude models in which the sum of the values exceeded the sum of the variances for all variables. All the results are presented as 2-tailed values with statistical significance for p values < 0.05.

RESULTS

Because of adverse events (2 injection site reactions and 1 recurrent infectious disease), 3 patients with PsA stopped the TNF-α blocker treatment prior to completing the 12-month followup. Nine control subjects missed the 12-month followup visit. Thus, 48 patients with PsA and 42 controls completed the 12-month followup and were included for analysis; their baseline clinical and demographic characteristics are reported in Table 1.

All the 48 patients with PsA who had active disease at the time of enrollment. Their mean disease duration was 9.08 ± 5.9 years. Twenty-four (50.0%) received etanercept, 18 (37.5%) adalimumab, and 6 (12.5%) infliximab. As many as 36 (75.0%) received concomitant treatment with MTX 10 mg/week; no variation in dosages was performed during the observation period.

During the 12-month followup, no significant changes occurred in the treatment of case and control subjects

Table 1. Baseline demographic and clinical characteristics of psoriatic arthritis (PsA) case and control populations.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PsA, n = 48</th>
<th>Controls, n = 42</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs, ± SD</td>
<td>50.96 ± 9.86</td>
<td>54.29 ± 11.49</td>
<td>0.143</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>24 (50.0)</td>
<td>18 (42.9)</td>
<td>0.531</td>
</tr>
<tr>
<td>Impaired fasting glucose (%)</td>
<td>14 (29.2)</td>
<td>16 (38.1)</td>
<td>0.382</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>26 (54.2)</td>
<td>16 (38.1)</td>
<td>0.144</td>
</tr>
<tr>
<td>Hypertiglyceridemia (%)</td>
<td>16 (33.3)</td>
<td>12 (28.6)</td>
<td>0.655</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>14 (29.2)</td>
<td>7 (16.7)</td>
<td>0.087</td>
</tr>
<tr>
<td>Smoking habit (%)</td>
<td>10 (20.8)</td>
<td>10 (23.8)</td>
<td>0.802</td>
</tr>
<tr>
<td>MetS (%)</td>
<td>18 (37.5)</td>
<td>14 (33.3)</td>
<td>0.826</td>
</tr>
<tr>
<td>ESR</td>
<td>24.13 ± 14.17</td>
<td>10.86 ± 3.26</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CRP</td>
<td>3.29 ± 4.70</td>
<td>0.98 ± 0.60</td>
<td>0.002</td>
</tr>
<tr>
<td>Hepatic steatosis (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>30 (62.5)</td>
<td>20 (47.6)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>14 (29.2)</td>
<td>18 (42.9)</td>
<td>0.348*</td>
</tr>
<tr>
<td>Severe</td>
<td>4 (8.3)</td>
<td>4 (9.5)</td>
<td></td>
</tr>
</tbody>
</table>

*p for trend. MetS: metabolic syndrome; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.
regarding statins and omega-3 fatty acid intake. Compared with baseline values, no significant changes in serum cholesterol (from 194.52 ± 35.1 to 193.43 ± 36.35 mg/dl; p = 0.734), serum triglycerides (from 134.50 ± 56.90 to 141.34 ± 55.71 mg/dl; p = 0.144), and body weight (from 80.93 ± 11.73 to 82.40 ± 11.96 kg; p = 0.076) were found at 12-month followup.

On the US evaluations (Table 1), 50/90 subjects showed a mild HS (Grade 1), 32/90 moderate HS (Grade 2), and 8/90 severe HS (Grade 3). No difference was found between patients with PsA and controls for HS baseline score (1.46 ± 0.65 vs 1.62 ± 0.66, respectively; p = 0.249).

The distribution of HS grades detected at 12-month US evaluation is shown in Figure 1. Compared with baseline (T0) evaluation, HS grade did not worsen in 34/50 subjects with mild HS; it reached Grade 2 in 14/50 and Grade 3 in 2/50. Among those (n = 32) with moderate HS at T0, 22 did not show disease worsening and 10 reached a grade of 3. Worsening of the HS score was found in 20 (41.7%) patients with PsA and in 6 (14.3%) controls (p = 0.005). Whereas mean HS scores of controls changed little (1.62 ± 0.66 at T0; 1.71 ± 0.83 at T1; p = 0.157), a significant worsening was found in patients with PsA (1.46 ± 0.65 at T0; 1.78 ± 0.78 at T1; p = 0.003), and the grade of worsening was higher in patients with PsA compared to controls (0.37 ± 0.70 vs 0.09 ± 0.43, respectively; p = 0.028). The percentage of patients with PsA who had worsening HS was similar between those with and those without concomitant treatment with MTX (44.4% vs 33.3%; p = 0.734), serum triglycerides (from 134.50 ± 56.90 to 141.34 ± 55.71 mg/dl; p = 0.144), and body weight (from 80.93 ± 11.73 to 82.40 ± 11.96 kg; p = 0.076) were found at 12-month followup.

DISCUSSION

MDA is defined by the Outcome Measures in Rheumatology Clinical Trials as “that state of disease activity deemed a useful target of treatment by both the patient and the physician, given current treatment possibilities and limitations.” Such a definition of MDA encompasses both remission and low disease activity, includes the evaluation of joints, skin, entheses, and patient-reported outcomes, and provides useful criteria and outcome measures for clinical trials.

In addition to the ability to foster achievement of MDA, TNF-α blockers improve the MetS-mediated poor vascular profile of subjects with PsA. TNF-α is likely to cause HS and liver damage by activating the proapoptotic protein Bax, in a c-jun N-terminal kinase-dependent manner. A higher than normal prevalence of liver steatosis has been reported in patients with PsA. On the other hand, a favorable clinical outcome is described in patients with non-alcoholic steatohepatitis receiving TNF-α blockers for concomitant rheumatic disorders. We report that patients with PsA who did not have MDA showed a significantly greater progression of HS than controls and PsA patients achieving MDA.

Worsening of the HS score was found in 20 (41.7%) patients with PsA and in 6 (14.3%) controls (p = 0.005). Whereas a correlation between psoriasis and liver steatosis is well established, the extent of a correlation between changes in PASI score and in degree of liver steatosis in patients with PsA is poorly understood. At T1, we found a significant improvement in mean PASI score as compared with T0 (from 2.13 ± SD 0.77 to 0.78 ± SD 0.87; p < 0.001).
After the 12-month treatment with TNF-α blockers, higher PASI values were found in those with worsening of HS compared to those with an unchanged/improved HS score (1.00 ± SD 0.80 vs 0.64 ± SD 0.90; p = 0.021). This prompted us to design a new study that compares changes of HS in patients with PsA to those with psoriasis. Results from this ongoing study will confirm and extend our present data, and will help address relevant issues in the area.

Some potential limitations of our study need to be addressed. The lack of a liver biopsy for the diagnosis of HS may hamper the relevance of our findings. However, in spite of its inherent operator dependence, abdominal ultrasound analysis is currently thought to provide reliable, precise information about HS. This limits the need for liver biopsy to the diagnosis of nonalcoholic steatohepatitis and to staging the severity of hepatic fibrosis. Moreover, despite its limitations, US analysis has been validated against histopathological specimens as well as other imaging methods for the diagnosis of liver steatosis. Nevertheless, the question of whether TNF-α blockers prevent serious liver damage (i.e., cirrhosis) in the setting of PsA may require confirmation by liver biopsy.

Among current TNF-α blockers, significant molecular differences led to classification into at least 2 different categories. Etanercept is a human dimeric fusion protein that binds to TNF-α and inhibits its interaction with cell-surface receptors. Infliximab and adalimumab are monoclonal immunoglobulins (murine/human chimeric and fully humanized, respectively) that inhibit binding of TNF-α to its receptor. As for liver toxicity, literature data suggest a better safety profile for etanercept than infliximab, although this is challenged. Of the 48 subjects with PsA, 24 (50%) were receiving etanercept and 24 (50%) infliximab or adalimumab, and none reported liver toxicity. Thus, this variable cannot be evaluated in our sample. As for HS worsening, after stratifying our results according to the drug used, no differences were found in the different treatment settings. However, the relatively small sample size may have hampered the possibility of identifying differences between the 2 drugs. Similarly, because of the sample size, stratification of results according to the progressive magnitude of improvement of disease activity (from T0 to T1) in patients who did not have MDA was unlikely. Thus, our results must be considered just a proof of concept.

MTX-induced hepatotoxicity (incidence 7.5%–9.3%), with a severity ranging from mild elevation in transaminases to hepatic failure, is a known clinical entity. As HS had been documented in all subjects enrolled in our study, a low dose of MTX (mean 10 mg/week) was used in our setting according to studies on combination treatments in PsA. When we compared the HS worsening in those who received MTX and in those who did not, similar results were found (p = 0.737).

No significant changes in plasma levels of serum cholesterol or triglycerides, body weight, or in treatment with statins and/or omega-3 fatty acids occurred during the 12-month followup. In addition, the regression analysis was adjusted for all these covariates as well as for the duration of rheumatic disease. Thus, changes of HS are unlikely to be due to the potential interference of these variables.
Our study first shows that better control of the inflammatory process of patients with PsA is correlated to less US worsening of HS. The extent to which the observed effect is mediated by TNF-α blockers remains unclear, and cannot be ruled out based on these data. Larger studies are needed to address this relevant issue.

APPENDIX

List of study collaborators. CaRRDs (Cardiovascular Risk in Rheumatic Diseases) study group: Paolo Osvaldo Rubba, Biagio De Simone, Marco Gentile, Department of Experimental and Clinical Medicine, Atherosclerosis Prevention and Vascular Medicine Unit, Federico II University, Naples, Italy.

REFERENCES