Evaluation of serum biomarkers of fibrosis and injury in Egyptian patients with chronic hepatitis C

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Background/Aims: We evaluated whether surrogate serum biomarkers for liver injury are comparable to liver biopsy in Egyptian patients with hepatitis C virus (HCV) infection.

Subjects: Two hundred and twenty Egyptian patients, 91% infected with genotype-4 HCV, undergoing liver biopsy during evaluation for interferon/ribavirin therapy.

Methods: Liver biopsy scored by the Ishak method was compared to biochemical tests, platelet count and two fibrosis biomarkers: hyaluronic acid (HA) and YKL-40. Univariate and logistic regression analyses determined independent predictors of fibrotic, inflammatory, and fatty changes. Biomarkers were evaluated for ability to differentiate between severe fibrosis/cirrhosis and no/mild fibrosis.

Results: Although increasing age, HA, YKL-40, AST, reduced platelet count, and AST and HA/platelet count ratios were associated with fibrosis by univariate analysis, the other variables were not significant after controlling for HA (p = 0.0001) and age (p = 0.004). Although age and some biomarkers were associated with inflammation, none remained significant after controlling for fibrosis. YKL-40 (p = 0.04) and aspartate aminotransferase (p = 0.05) remained associated with steatosis after controlling for fibrosis.

Conclusions: In Egyptians with chronic HCV, young patients with low levels of HA are at very low risk of fibrosis. This can limit the number of liver biopsies to those whose clinical findings conflict with the biomarker results.

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Keywords: Hepatitis C virus; HCV; Fibrosis; Cirrhosis; Morbidity assessment; Liver biopsy; Serum hepatic fibrosis markers; Hyaluronic acid; YKL-40

Received 30 May 2006; received in revised form 5 December 2006; accepted 13 December 2006; available online 24 January 2007

* The authors who have taken part in this study declared that they have no relationship with the manufacturers of the drugs involved either in the past or present and received funding from WellcomeTrust and Schering-Plough.

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1. Introduction

We rely on repeated liver biopsies with their associated risks, cost, and sampling errors to detect, grade, and monitor hepatic pathology in hepatitis C (HCV) infections and other chronic liver diseases [1–6]. It is difficult to justify serial liver biopsies to diagnose and monitor patients with chronic HCV when there are limited options for managing their disease, as is the usual case in Egypt [7].

Noninvasive reliable biomarkers for diagnosing and grading hepatic fibrosis and to monitor outcome of treatment and the course of HCV infection are an active area of clinical interest [3,4,8–22]. This study’s objective was to evaluate individually and in combination the ability of routine laboratory tests and two serum biomarkers of extracellular matrix to predict hepatic fibrosis, inflammation and steatosis and compare them with liver biopsy findings in Egyptian patients being evaluated for a clinical trial comparing antiviral therapy for genotype-4 HCV.

2. Methods

2.1. Patients

This cross-sectional study included 220 adults with chronic HCV infections being evaluated for a randomized clinical trial to compare two interferon and ribavirin regimens at the National Hepatology and Tropical Medicine Research Institute in Cairo, Egypt. All gave their informed consent, which included undergoing a pretreatment liver biopsy. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was reviewed and approved by the Egyptian Ministry of Health and Population’s, University of Maryland-Baltimore’s, and Walter Reed Army Medical Center’s Institutional Review Boards. Prior to acceptance in the treatment trial, all subjects were screened for schistosomiasis and treated with praziquantel if they had ova in their stools or urine. Four individuals had schistosoma granuloma, evidence of previous infection with Schistosoma mansoni, detected on their liver biopsies.

Diagnosis of chronic HCV was established by elevated alanine aminotransferase enzyme (ALT) levels in persons having HCV antibody (anti-HCV) by a third generation enzyme immunoassay (EIA) and HCV-RNA using an in-house direct reverse transcriptase polymerase chain reaction (RT-PCR) assay [23]. Patients were excluded if they had other causes of chronic liver diseases, including chronic hepatitis B, or previously received interferon therapy. All patients denied intravenous drug abuse and four patients reported they consumed about 200 g of alcohol daily. Patients were all screened for hepatitis C genotype types 2, 3 and 4, with 57% being genotype 4.

Study subjects included the 200 patients enrolled in the treatment trial and 20 others screened but not enrolled having stage 1, 2, 5 and 6 Ishak fibrosis scores. We included a second control population of 88 HCV patients at Beth Israel Deaconess Medical Center in Boston for validation of our findings.

2.2. Survey and laboratory data

A previously validated questionnaire was used to collect demographic and medical information. Laboratory test results used in this report, serum ALT, aspartate aminotransferase (AST), alkaline phosphatase (ALP), total and direct bilirubin, and blood platelet counts, were all performed using standard methods. Serum hyaluronic acid (HA; Corgenix, Denver, CO) and YKL-40 (Metra, Biosystems, Mound View, CA) were measured using commercially available bioassays. The ALT and AST indexes were calculated by dividing the patient’s test result by the upper limit of normal for the test. The AST/platelet count ratio index (APRI) was calculated as AST index/platelet count divided by 103 times 100. The HA/platelet count ratio was calculated as the HA level/platelet count divided by 103 times 100.

2.3. Liver biopsy

These were examined by a hepatopathologist (KRZ) blinded to patient characteristics. All biopsy cores were at least 1 cm in length and encompassed at least three portal areas. The scoring system of Ishak et al. (modified HAI and staging) was used to assess fibrosis stage and necroinflammatory injury [24]. Necroinflammatory activity was classified into mild (score 1–5), moderate (score 6–8), and severe (score 9–18). Fibrosis was staged separately on a scale of 0–6. Stages 0–1 indicated no or mild fibrosis, stages 2- and -3 moderate fibrosis, and 4-6 more severe fibrosis or cirrhosis. Macrophage infiltration was classified into grades: 0 (no fatty infiltration), 1 (up to 33% of hepatocytes affected), II (greater than 33-66% of hepatocytes), and III (greater than 66% of hepatocytes) [25].

2.4. Statistical analysis

Patients were classified according to their stage of fibrosis, inflammation, or steatosis as noted on liver biopsy. Box plots were used to show distribution of different biomarkers in relation to stages of fibrosis. Univariate logistic regression was used to assess the association between biomarker levels and severe fibrosis or cirrhosis, inflammation or steatosis. Multiple logistic regression was used to assess the association between biomarkers and outcomes, while controlling for other variables.

Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values were calculated for predicting severe fibrosis and cirrhosis (stages 4-6), moderate or severe inflammatory changes (grade 6 or more), and grade II or III fatty infiltration. Receiver operating characteristic curves (ROC) were constructed to assess the power of the biomarkers in predicting severe and mild hepatic fibrosis by calculating the area under the curve.

3. Results

The 220 subjects were predominately (79%) male with a mean age of 39.3 years; 91% were infected with genotype 4 HCV (Table 1). Severe hepatic fibrosis was present in 23%; 59% had mild-to-moderate fibrosis, while 18% had mild or no fibrosis; 49% of biopsies were read as moderate grades of necroinflammatory changes; 29% had minimal inflammation; while 22% had severe inflammation. No steatosis was present in 43%; 39% had minimal steatosis (grade I); and 18% had grade II and III steatosis (Table 1). There was a strong relationship (p < 0.001) between stage of fibrosis and necroinflammatory changes, but not between fibrosis and steatosis; 77.5% of biopsies with mild or no fibrosis had Ishak grade 1–5 inflammatory changes while 57% of biopsies with moderate-to-severe fibrosis or cirrhosis had Ishak grade 9–18 inflammatory changes (Table 2).

3.1. Association of the biomarkers with hepatic fibrosis

Univariate analysis showed that older age, but not gender, was associated with stage of fibrosis (Table 2).
Comparisons with demographic and laboratory parameters showed increase in age (p < 0.0001), HA (p < 0.0001), HA/platelet count ratio (p < 0.0001), YKL-40 (p < 0.0001), APRI (p = 0.0007) and AST (p = 0.009) was all associated with the level of fibrosis. In addition, the platelet count was inversely related (p = 0.0004) to fibrosis. Neither the ALT (p = 0.063), ALP (p = 0.17), nor total (p = 0.22) or direct (p = 0.089) bilirubin levels were associated with hepatic fibrosis. In addition, combinations of test results, other than APRI, did not improve the predictive value of individual tests.

When age and the biomarkers were included in a forward stepwise logistic regression model, only age (p = 0.004) and HA (p < 0.0001) were significantly associated with severe fibrosis or cirrhosis. Table 3 shows the sensitivity, specificity, and PPV and NPV of the biomarkers for predicting stage 4–6 fibrosis using convenient cut-off levels in which 23% of biopsies were graded as stages 4–6. HA levels of 20 ng/ml or greater had a sensitivity of 88%, a specificity of 68%, and PPV and NPV of 45% and 95%, respectively. These results are slightly superior to those of the YKL-40 and the APRI, and are about the same as those for the HA/platelet count ratio with a cut-off of 10.

Fig. 1 shows the median 50th percentile (in the box) and 25th and 75th percentile (in the whiskers) for six biomarkers as they relate to hepatic fibrosis. Although there was considerable overlap, in the case of HA, YKL-40, AST, HA/platelet count ratio, and APRI, the median and 50th percentile of each group increased progressively with increasing stages of fibrosis and the median and 50th percentile of the platelet count decreased with increasing fibrosis. Despite overlap with

**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>Egyptian N (%)</th>
<th>American N (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>39.3 ± 8.7</td>
<td>50.4 ± 7.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male gender</td>
<td>173 (78.6)</td>
<td>59 (65.6)</td>
<td>0.016</td>
</tr>
<tr>
<td>BMI (mean ± SD)</td>
<td>27.9 ± 4.0</td>
<td>26.8 ± 4.4</td>
<td>0.052</td>
</tr>
<tr>
<td>HCV genotype</td>
<td>175 (90.7)</td>
<td>2 (3.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ALT ratio above upper limits normal (mean ± SD)</td>
<td>1.76 ± 1.05</td>
<td>2.05 ± 1.85</td>
<td>0.16</td>
</tr>
<tr>
<td>AST ratio above upper limits normal (mean ± SD)</td>
<td>1.74 ± 1.2</td>
<td>1.58 ± 1.56</td>
<td>0.37</td>
</tr>
<tr>
<td>Alkaline phosphatase (ALP)</td>
<td>101.3 ± 39.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count (mean ± SD)</td>
<td>219.8 ± 66.5</td>
<td>224 ± 74.5</td>
<td>0.64</td>
</tr>
</tbody>
</table>

**Fibrosis**
- Stages 0–1: 40 (18.2)
- Stages 2–3: 129 (58.6)
- Stages 4–6: 51 (23.2)

**Necroinflammation**
- Grades 1–5: 64 (29.1)
- Grades 6–8: 107 (48.6)
- Grades 9–12: 49 (22.3)

**Steatosis**
- Grade 0: 93 (42.9)
- Grade I: 84 (38.7)
- Grades II and III: 40 (18.4)

**Table 2**

<table>
<thead>
<tr>
<th>Fibrosis stages</th>
<th>Stages 0–1 number (%)</th>
<th>Stages 2–3 number (%)</th>
<th>Stages 4–6 number (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>40 (18.2)</td>
<td>129 (58.6)</td>
<td>51 (23.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>36.4 ± 7.4</td>
<td>38.4 ± 8.7</td>
<td>43.9 ± 7.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>31 (77.5)</td>
<td>100 (77.5)</td>
<td>42 (82.4)</td>
<td>0.76</td>
</tr>
<tr>
<td>HCV Genotype</td>
<td>18/20 (90)</td>
<td>113/125 (90.4)</td>
<td>44/48 (91.7)</td>
<td>0.96</td>
</tr>
<tr>
<td>Inflammatory changes</td>
<td>Grades 1–5</td>
<td>31 (77.5)</td>
<td>30 (23.3)</td>
<td>3 (5.9)</td>
</tr>
<tr>
<td></td>
<td>Grades 6–8</td>
<td>8 (20.0)</td>
<td>80 (62)</td>
<td>19 (37.3)</td>
</tr>
<tr>
<td></td>
<td>Grades 9–12</td>
<td>1 (2.5)</td>
<td>19 (14.7)</td>
<td>29 (56.9)</td>
</tr>
<tr>
<td>Steatosis</td>
<td>Grades 0</td>
<td>12 (30)</td>
<td>56 (44.1)</td>
<td>25 (50)</td>
</tr>
<tr>
<td></td>
<td>Grades I</td>
<td>20 (50)</td>
<td>48 (37.8)</td>
<td>16 (32)</td>
</tr>
<tr>
<td></td>
<td>Grades II and III</td>
<td>8 (20)</td>
<td>23 (18.1)</td>
<td>9 (18)</td>
</tr>
</tbody>
</table>

* Data from 27 Egyptians missing.

* Data from 3 Egyptians missing.
Table 3

Sensitivity, specificity and positive (PPV) and negative (NPV) predictive values of different biomarkers to diagnose severe fibrosis or cirrhosis (stages 4–6) based on its observed prevalence of 23%

<table>
<thead>
<tr>
<th>Cut-off value for biomarkers</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyaluronic acid (HA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.98</td>
<td>0.39</td>
<td>0.33</td>
<td>0.99</td>
</tr>
<tr>
<td>20</td>
<td>0.88</td>
<td>0.68</td>
<td>0.45</td>
<td>0.95</td>
</tr>
<tr>
<td>140</td>
<td>0.22</td>
<td>0.96</td>
<td>0.65</td>
<td>0.80</td>
</tr>
<tr>
<td>YKL- 40</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>1.00</td>
<td>0.08</td>
<td>0.25</td>
<td>1.00</td>
</tr>
<tr>
<td>100</td>
<td>0.82</td>
<td>0.57</td>
<td>0.37</td>
<td>0.92</td>
</tr>
<tr>
<td>400</td>
<td>0.20</td>
<td>0.96</td>
<td>0.63</td>
<td>0.80</td>
</tr>
<tr>
<td>AST index/platelet count ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td>1.00</td>
<td>0.04</td>
<td>0.24</td>
<td>1.00</td>
</tr>
<tr>
<td>0.6</td>
<td>0.86</td>
<td>0.53</td>
<td>0.36</td>
<td>0.93</td>
</tr>
<tr>
<td>2.0</td>
<td>0.17</td>
<td>0.95</td>
<td>0.56</td>
<td>0.80</td>
</tr>
<tr>
<td>HA/platelet count ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>0.98</td>
<td>0.37</td>
<td>0.32</td>
<td>0.98</td>
</tr>
<tr>
<td>10.0</td>
<td>0.84</td>
<td>0.69</td>
<td>0.45</td>
<td>0.94</td>
</tr>
<tr>
<td>75.0</td>
<td>0.29</td>
<td>0.95</td>
<td>0.65</td>
<td>0.82</td>
</tr>
</tbody>
</table>

We also analyzed the data comparing the different biomarkers to hepatic fibrosis using ROC. The results confirmed that HA, HA/platelet count ratio, YKL-40 and APRI were predictive of level of hepatic fibrosis. When predicting more severe fibrosis or cirrhosis (stages 4–6), the areas under the curves were 0.84 for HA/platelet count ratio, 0.83 for HA, 0.74 for APRI, and 0.74 for YKL-40. When ROC was used to differentiate no/mild fibrosis (stage 0–1) from stage 2 to 6 fibrosis the areas under the curve were 0.73 for HA/platelet count ratio, 0.73 for HA, 0.62 for YKL-40 and 0.59 for APRI.

3.2. Association of biomarkers with hepatic inflammation

HA (p = 0.007), YKL-40 (p = 0.009), and HA/platelet count (p = 0.02) and APRI (p = 0.03) ratios predicted the levels of necroinflammatory changes in hepatic biopsies using univariate analyses. However, when adjusted for fibrosis (Table 2), none were significantly associated with inflammatory changes.

3.3. Association of biomarkers with hepatic steatosis

YKL-40 and AST were associated with grades of steatosis by univariate analyses; and they remained significant after adjusting for fibrosis (p = 0.036 and p = 0.046, respectively). The odds of presence of stage II or III fatty infiltration doubled when YKL-40 level was 100 or more (OR = 2.0, 95% CI = 0.95–4.25, p = 0.06). Table 4 shows the sensitivity, specificity and predictive values of different levels of YKL-40, AST index and YKL/AST index ratio in predicting grade II or III steatosis. HA levels were not associated (p = 0.30) with hepatic steatosis.

3.4. Clinical utilization of serum biomarkers for assessing hepatic injury in Egyptian patients

Only 5 (4.5%; 95% CI = 1.5–10.2%) of 111 patients under age 45 with HA levels less than 30 had severe fibrosis or cirrhosis. Thus, such patients could be viewed at low risk for chronic complications and the clinician could follow them at intervals without performing a liver biopsy. On the other hand, 17/25 (68%; 95% CI = 46–86%) among those with HA of 100 or greater who were 40 or older had severe fibrosis or cirrhosis. Such patients should be considered at high risk for cirrhosis and its complications and candidates for further diagnostic and therapeutic interventions, with or without a confirmatory liver biopsy. Eighty-three (37.7%) patients could not be classified by our algorithm using HA and age. They would require additional studies, including a liver biopsy if clinically indicated.

3.5. American patients

We analyzed results in a cohort of 88 American patients having biopsies and serum biomarker data. These patients were somewhat older, less likely to be male, had a slightly lower BMI, more likely to have mild than moderate fibrosis, and as expected, only two had genotype-4 infections (Table 1). Generally similar, but less strong, associations were found between the biomarkers and fibrosis in the Americans. For example, of those with an HA less than 30, 6/46 (13%) had severe fibrosis or cirrhosis, whereas, 12/23 (52%) of those with an HA over 100 had severe fibrosis or cirrhosis. The biomarkers with the strongest associations with fibrosis were decreased in platelets (p = 0.0003) and increased in the HA level (p = 0.01).

4. Discussion

Noninvasive methods to measure severity of liver injury are clinically important in Egypt where advanced liver disease from HCV is common and access to liver biopsy is limited [7,26,27]. In addition, reliability of the biopsy to detect and measure hepatic pathology is not ideal [3,5,6,28]. For instance, in a multicenter study validating biochemical markers for predicting liver fibrosis in patients with chronic HCV, the authors proposed discordance caused by interpretation of the biopsy (4%) as frequent as in the Fibrotest (5%) being evaluated [4]. Many of the reports evaluating biomarkers for detecting hepatic fibrosis have used scoring systems encompassing combinations of results.
from several blood tests and demographic data [4,9,12,13,17,20,22,29].

Most of the indexes proposed in these studies would not be practical in Egypt and other developing countries because of cost and unavailability of some tests. For this reason we evaluated a few blood tests routinely performed on patients with chronic HCV in Egypt in addition to two commercially available tests for measuring hepatic fibrosis. Predictability of hepatic injury was not significantly improved when we evaluated combinations of results from two or more tests. Thus, we believe that we present a useful, practical and cost-effective approach for using serum biomarkers of hepatic fibrosis, inflammation and steatosis in Egypt and other areas with limited resources.

Prior studies of serum biomarkers for HCV in developed countries have arbitrarily chosen to stratify for no or mild fibrosis (Metavir F0/1 or Ishak F0-2) compared...
to moderate/advanced disease (Metavir F2-4 or Ishak F3-6) since F2 is the point at which interferon therapy is usually offered. Other experts state that biomarkers have a greater role, and higher sensitivity in diagnosing advanced disease, and particularly cirrhosis (Metavir F3/4 or Ishak F4-6). This is particularly important in Egypt where there is a heavy chronic liver disease burden since diagnosing severe fibrosis or cirrhosis could initiate strategies for treatment of HCV and screening for hepatocellular carcinoma. Time of exposure to HCV is known only in a few of our patients. Their mean age of 39 years suggests that as many as half were infected as children during treatment campaigns for schistosomiasis 20–40 years earlier [7,30].

In a multicenter study in 486 patients with chronic HCV undergoing liver biopsy, the clinical value of HA measurement was its ability to exclude cirrhosis [14]. A HA value of less than 60 ng/L excluded cirrhosis or significant fibrosis in their patients with a NPV of 99% and 93%, respectively. Oberti et al. evaluated markers of fibrosis in 243 patients [16]. HA performed the best of the four being evaluated having a diagnostic accuracy of 86% for detecting cirrhosis in subpopulations having viral or combined viral and alcoholic etiologies. Wong et al. showed that HA had 85% sensitivity and 88% specificity for predicting stage 4 and 5 fibrosis [8]. More recently, Kelleher et al. developed the SHASTA index, using HA, age and albumin, to differentiate mild from advanced fibrosis in patients co-infected with HCV and HIV [13]. Patel and colleagues reported a panel of HA, TIMP-1, and alpha2-macroglobulin had about a 75% PPV and NPV in differentiating moderate/severe fibrosis from no/mild fibrosis in almost 700 patients with chronic HCV infection [22]. Furthermore, HIV co-infection did not reduce the value of noninvasive biomarkers to detect and measure fibrosis in HCV infected patients [31].

HA was our optimal single test for predicting fibrosis. A HA level of less than 30 ng/ml among those under 45 years of age excluded severe fibrosis or cirrhosis with a NPV of 95%. Using HA would have saved performing liver biopsies in more than half of our patients. One caveat regarding this calculation is that the NPV will vary depending on the prevalence of fibrosis in the patient population.

We have focused on presenting a practical noninvasive and inexpensive alternative to liver biopsy for assessing hepatic injury in Egyptian patients with chronic HCV infections. However, it is customary to validate the conclusion from studies such as this in a second group of patients. Results from a cohort of American patients with chronic HCV show that our conclusions are valid, albeit with less reliability.

In addition to diagnosing cirrhosis, biomarkers have value if they also detect severe inflammation or steatosis. The risk of disease progression has been shown to be dependent on the grade of inflammation on biopsy [32]. Most previous studies reported HA levels could not predict grade of hepatic inflammation. However, Ishibashi et al. reported HA levels correlated with inflammatory changes in their patients’ biopsies [10]. Our initial analysis also showed that HA and YKL-40 levels could predict hepatic inflammation, but after adjusting for fibrosis, these associations were not statistically significant. Serum ALT has long been a surrogate for inflammation and until better markers are determined it will probably remain the most widely used test. Although our study did not show a relationship between ALT values and the necroinflammatory grades, an ALT level of 200 IU/L or greater may be associated with increased risk of HCV disease progression [33].

The prevalence of steatosis in our Egyptian patients infected with genotype 4 HCV, 57%, is close to the average of 55.5% reported in chronic HCV [34]. Unlike our findings, steatosis has correlated with fibrosis in other cross-sectional studies of patients with HCV. The very little consumption of alcohol among our almost exclusively Muslim population may explain this difference since alcohol is believed to increase steatosis in patients with chronic HCV [35], or the relationship between fibrosis and steatosis is less in patients infected with genotype 4 than those infected with other genotypes. Steatosis has been reported to reduce therapeutic response to antiviral therapy in patients with chronic HCV [34,36]. There was a significant reduction in sustained viral clearance among our 200 patients having grade II and III hepatic steatosis who were treated with interferon and ribavirin (unpublished, Esmat G). Our finding that both YKL-40 and AST remained predictive for grade II and III steatosis, even after adjusting for hepatic fibrosis, should be further evaluated.

In addition to reliability issues, routine liver biopsy for following HCV infected patients in a country like Egypt is expensive and impractical. Therefore, an effective surrogate test to stage hepatic fibrosis that
is inexpensive, reproducible and simple to perform is highly desired. The combination of HA, YKL-40, platelet count, and transaminases appeared adequate to achieve this cost-effectively, and also provided information about the amount of hepatic inflammation and steatosis in our Egyptian patients. In Egypt, with limited resources but almost twice the number of people with chronic HCV infections as in the USA [7,30], these serum biomarkers, particularly HA, can assist the clinician in making prognostic and therapeutic decisions. They can provide guidance as to whether the patient has minimal hepatic fibrosis or more severe lesions, and in many cases replace the need for a liver biopsy with a simple blood test. However, they must be evaluated in cohorts of HCV patients being prospectively followed to determine whether HA or other serum biomarkers can predict hepatic disease progression and its clinical outcome.

Acknowledgements

We thank Dr. Maria Sjogren of Walter Reed Army Medical Center in Washington, DC, who arranged funding from Schering-Plough Corporation and provided advice for the randomized clinical trial for which the liver biopsies were performed. Professor Alaa Ismail, Dean of the National Hepatology and Tropical Medicine Research Institute, provided support and advice. Financial support: This work was partially funded by Schering-Plough Corporation and Wellcome Trust-Burroughs Wellcome Fund Infectious Diseases Initiative Grants 059113/Z/99/A and 059113/13/Z/99/Z.

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