Hepatitis C virus infection and lichen planus: a systematic review with meta-analysis

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OBJECTIVE: Hepatitis C virus (HCV) is one of the major causes of chronic liver disease worldwide but its morbidity is also due to a variety of extra-hepatic manifestations including mixed cryoglobulinemia, non-Hodgkin lymphoma, diabetes, porphyria cutanea tarda and lichen planus. The aims of this study were to conduct a systematic review and a meta-analysis on the prevalence of HCV in lichen planus patients and on the prevalence of lichen planus in chronic HCV infection.

MATERIALS AND METHOD: Bibliographic searches were conducted in several electronic databases. Pooled data were analysed by calculating odds ratios, using a random effects model.

RESULTS AND CONCLUSIONS: Thirty-three studies comparing the seroprevalence of HCV in lichen planus patients and six reporting the prevalence of lichen planus in patients with HCV infection were included in the meta-analysis. The summary estimate showed that LP patients have significantly higher risk (odds ratio 4.85; 95% confidence interval 3.58–6.56) than controls of being HCV seropositive. A similar odds ratio of having lichen planus was found among HCV patients (4.47; 95% confidence interval 1.84–10.86). Sub-analyses indicated that variability of HCV/lichen planus association seemed only partially depending on geographic effect.

Keywords: lichen planus; oral lichen planus; hepatitis C virus; meta-analysis

Introduction

Hepatitis C virus (HCV) is presently considered as the main etiologic agent of both blood-borne and sporadic non-A and -B hepatitis, and is one of the major causes of chronic liver disease worldwide. However, morbidity associated with HCV infection is due not only to the sequelae of chronic liver disease, but also to a variety of extra-heaptic manifestations (EHM). According to a recent review, mixed cryoglobulinemia is the only EHM in which the association with HCV has been demonstrated by both epidemiological and pathogenetic evidences, while diseases strongly suspected to be linked to HCV include B-cell non-Hodgkin lymphoma, monoclonal gammapathies, porphyria cutanea tarda and lichen planus (LP) (Zignego et al, 2007).

Lichen planus is a relatively common disorder of the stratified squamous epithelia frequently involving the oral cavity exclusively (Eisen et al, 2005).

A possible link between hepatitis viruses and LP has been suggested by the frequent association between LP and chronic liver disease (CLD) in Mediterranean patients (Carrozzo and Gandolfo, 2003) but no pathogenic correlation could be found until HCV assays became available. The risk of chronic liver disorders in LP patients is in fact independent from alcohol consumption, and is still significantly high after adjustment for a positive hepatitis B surface antigen (HBsAg) reaction (GISED, 1990). Markers of past hepatitis B virus (HBV) infection [antibodies to hepatitis B surface antigen (HBsAb) and to hepatitis B core antigen (HBCAb)] have been reported in Spanish and Italian patients with LP (Ayala et al, 1986; Delolmo et al, 1990; Carrozzo et al, 1996), but with prevalence quite close the
average figure in the Mediterranean area. Moreover, the recently discovered viruses, hepatitis G virus or TTV, are not associated with LP (Nagao et al, 1997; Lodi et al, 2000; Bez et al, 2001; Rodriguez-Inigo et al, 2001).

When sensitive HCV diagnostic tests became available, a great amount of case reports (Carrozzo, 2008), cohort and controlled studies suggested a link between LP and HCV infection. A systematic review investigating HCV seropositivity in LP patients was published in 2004 (Lodi et al, 2004) and more than 20 controlled studies were published thereafter (Bokor-Bratic, 2004; Campisi et al, 2004; Chung et al, 2004; Denli et al, 2004; Harman et al, 2004; Karavelioglou et al, 2004; Asaad and Samdani, 2005; Dervis and Serez, 2005; Guerreiro et al, 2005; Laeijendecker et al, 2005; Luis-Montoya et al, 2005; Rahnama et al, 2005; Das et al, 2006; Sulka et al, 2006; Ali and Suresh, 2007; Amer et al, 2007; de Mattos Camargo et al, 2007; Ghaderi and Makhmalbaf, 2007; Giuliani et al, 2007; Yarom et al, 2007). Moreover, the frequency of LP in patients with HCV infection has never been reviewed systematically.

In recent reviews devoted to HCV-EHM, conflicting statements have been made, some supporting and others discharging the link between LP and such viral infection (Sene et al, 2004; Ali and Zein, 2005; Palekar and Harrison, 2005; Sterling and Bralow, 2006; Galossi et al, 2007; Okuse et al, 2007; Zignego et al, 2007; Carrozzo, 2008) but literature was rarely reviewed with a systematic approach.

Furthermore, IFN-α and ribavirin may cause or exacerbate some muco-cutaneous disorders (Berk et al, 2007), including LP, sometimes leading to anti-HCV treatment withdrawal (Protzer et al, 1993). As a result, it is difficult to determine whether LP results from HCV, IFN-α/ribavirin, both or neither. On the other hand, there are also some concerns about the inclusion of LP patients in clinical trial of IFN-α therapy (Berk et al, 2007).

The aim of our study was to systematically review epidemiological data on the association between HCV infection in LP. The two null hypotheses of our study were that (ii) there is no difference between the proportion/number of anti-HCV seropositive subjects in patients affected by LP compared with control groups, against the alternative hypothesis of a difference, and (ii) there is no difference between the proportion/number of subjects affected by LP in patients HCV seropositive compared with control groups, against the alternative hypothesis of a difference.

All along the text the term LP has been used generically to indicate both skin and oral LP (OLP). When a more specific indication was opportune, the more precise terminology of skin or cutaneous LP and OLP was used.

**Patients and methods**

**Criteria for considering studies**

Studies addressing the relationship between LP and HCV seropositivity were considered. We collected either studies investigating the prevalence of HCV in LP patients or studies assessing the frequency of LP in HCV seropositive and/or infected subjects. Studies were eligible for the inclusion in the meta-analysis when they fulfilled the following criteria:

1. analytical study design as indicated by Grimes and Schulz (Grimes and Schulz, 2002), i.e. an observational study with a comparison or control group;
2. diagnosis of LP based on clinical and histological features;
3. HCV seropositivity based on serological test for circulating anti-HCV antibodies

Exclusion criteria were the following:

1. Studies involving patients with HCV and HIV co-infection
2. Studies where HCV could not be excluded from other causes of liver disease
3. Studies using references data or data from blood donors banks or historical controls
4. Duplicate studies (studies originating from the same subjects by the same investigators but published in different journals)
5. Articles providing insufficient information to calculate the OR

**Search strategy for identification of studies**

To identify relevant literature, bibliographical searches were performed in PubMed (January 1966 to November 2007), EMBASE (January 1988 to November 2007) CINAHL (January 1982 to November 2007) and SCOPUS (January 1960 to November 2007) databases using the following terms: ‘Hepatitis C’, ‘Hepacivirus’, ‘HCV’, ‘lichen planus’ and ‘lichen*’. To identify additional studies, references lists of previously identified published papers were searched and the World Wide Web was searched by means of a search engine (http://www.google.com). The title and abstract of each article resulting from the literature search were independently reviewed by two investigators and when the article was considered relevant, the full report was obtained. Disagreements about eligibility were resolved by consensus with a third reviewer. Articles published in any language were included.

**Methods of the review**

**Selection of studies and assessment of study quality.**

Every study included was assessed on the basis of: (i) characteristics of the study group (consecutive, unselected patients); (ii) appropriateness of the control group; subjects belonging to the control group must not differ importantly from those of the study group (sex and age must be matched, subjects of the control group must be selected from the study base); and (iii) prospective design (i.e. data and sera collected on purpose). Each of these criteria was rated as ‘met’, ‘unmet’ or ‘unclear’. The global validity of the study was assessed using three categories: (i) low risk of bias: all criteria met; (ii) moderate risk of bias: one or two criteria unclear; and (iii) high risk of bias: at least one criterion unmet or three criteria unclear. The critical
Data about the study, its eligibility, validity, design and outcome information, were recorded on an abstraction form.

Data extraction and statistical analysis. For each study, data on the numbers of subjects of the study group and the control group with a positive outcome (HCV seropositive among LPs, and LP among HCV seropositives), were extracted. For each study an OR and 95% CI was calculated. Where absence of events in one of the groups caused problems with computation of OR, 0.5 was added to all values for that study, except when absence of events involved both study and control groups, in which case OR was undefined (Deeks et al., 2001). Heterogeneity was measured calculating I², a statistic for quantifying inconsistency among studies. However, as heterogeneity among studies was expected on the basis of a large variability in HCV prevalence across different countries, a random effect was used to calculate the summary estimate.

Subgroup analysis was undertaken for geographical area, patients with oral lesions, age, studies excluding lichenoid reactions and researches including a confirmatory HCV test further to the screening one. Sensitivity analysis was undertaken excluding studies of lower methodological quality (i.e. studies at moderate and high risk of bias). To investigate potential for publication bias we checked for asymmetry of the funnel plot of the OR of the included studies. The statistical analysis was conducted using RevMan5, a copyrighted freeware developed by the Cochrane Collaboration, for preparing and maintaining reviews (http://www.cochrane-net.org/revman).

Results

From 447 articles identified with different search strategies, 97 potentially eligible studies were found, of them 70 studies worldwide investigated HCV seroprevalence among LP patients (Table 1) and 27 of them investigated the frequency of LP in patients with chronic HCV infection met the criteria to be included in the review (Figure 1).

HCV prevalence among LP patients

The overall prevalence of HCV in LP patients according to the 70 studies involving 6378 patients was 22.3%, with a high variability among and within countries (Table 1). Among these studies, 33 met our inclusion criteria and were considered for the systematic review (Cribier et al., 1994; Santander et al., 1994; Bellman et al., 1995; Gimenez-Arnau et al., 1995; Talei et al., 1995; Carrozzo et al., 1996; Sanchez-Perez et al., 1996; Dupin et al., 1997; Imhof et al., 1997; Serpico et al., 1997; Bagan et al., 1998; Ilter et al., 1998; Ingafou et al., 1998; Mignogna et al., 1998; Ibrahim et al., 1999; Issa et al., 1999; Tucker and Coulson, 1999; Kirtak et al., 2000;
...including psoriasis patients only. The other control groups were formed by dental patients (five studies), blood donors (four study), dental health care workers (two study), healthy subjects (two studies), patients with unrelated oral keratoses (two study), surgical patients (two studies), healthy subjects and dermatological patients (one study), HIV negative outpatients (one study); in two studies the origin of control group was not specified. The serological test adopted to detect circulating anti-HCV antibodies was a second generation ELISA in 14 studies and a third/fourth generation ELISA in 15; in four cases the characteristics of the test were not reported. Positive results were confirmed by means of another test in 14 studies (Table 2).

Critical appraisal of the included studies. On the basis of the criteria previously described, nine studies resulted at low risk of bias, 11 were judged at moderate risk of bias, and 13 at high risk of bias (Table 2). The first criterion was met in less of half the studies, since study group was clearly formed by consecutive, unselected patients with LP in only 15 of the 33 studies. Of the other two criteria, control group was adequately selected and matched in 20 cases and the study had a prospective design in 19. None of the studies published in form of letter or abstract was judged at low risk of bias.

Table 1 (Continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Lichen planus patients</th>
<th>Number of HCV+ subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanei et al, 1995</td>
<td>45</td>
<td>17</td>
</tr>
<tr>
<td>Tucker and Coulson, 1999</td>
<td>45</td>
<td>0</td>
</tr>
<tr>
<td>van der Meij and van der Waal, 2000</td>
<td>55</td>
<td>0</td>
</tr>
<tr>
<td>Yarom et al, 2007</td>
<td>62</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>6378</td>
<td>1420 (22.26%)</td>
</tr>
</tbody>
</table>

Characteristics of the included studies. The main characteristics of the 33 included studies are presented in Table 2. Nineteen out of 33 studies were from European countries, two from USA, two from Africa, six from Asia, two from Middle East and two from South America. Two studies were written in a language different from English: one in Portuguese and one in Italian.

Eleven included only patients with oral lesions, which were present in a variable proportion in most of the other studies. The control group was enrolled amongst dermatological patients in 12 studies, in one case some patients with potentially HCV associated dermatological conditions (porphyria cutanea tarda, cutaneous vaculitis and prurigo) were excluded, while another included psoriasis patients only. The other control groups were formed by dental patients (five studies), blood donors (four study), dental health care workers (two study), healthy subjects (two studies), patients with unrelated oral keratoses (two study), surgical patients (two studies), healthy subjects and dermatological patients (one study), HIV negative outpatients (one study); in two studies the origin of control group was not specified. The serological test adopted to detect circulating anti-HCV antibodies was a second generation ELISA in 14 studies and a third/fourth generation ELISA in 15; in four cases the characteristics of the test were not reported. Positive results were confirmed by means of another test in 14 studies (Table 2).
Table 2 Characteristics of the studies included in the meta-analysis investigating HCV prevalence in lichen planus patients

<table>
<thead>
<tr>
<th>Country</th>
<th>Reference</th>
<th>n</th>
<th>Oral lesions</th>
<th>n</th>
<th>Provenience</th>
<th>Screening</th>
<th>Confirmatory</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>Isaa et al, 1999</td>
<td>34</td>
<td>9/34</td>
<td>60</td>
<td>Blood donors</td>
<td>ELISA 3</td>
<td>Unspecified</td>
<td>High</td>
</tr>
<tr>
<td>France</td>
<td>Cribier et al, 1994</td>
<td>52</td>
<td>4/52</td>
<td>112</td>
<td>Dermatology patients</td>
<td>ELISA 2</td>
<td>RIBA 2</td>
<td>Moderate</td>
</tr>
<tr>
<td>Germany</td>
<td>Ibrahim et al, 1999</td>
<td>43</td>
<td>Unspecified</td>
<td>306</td>
<td>Surgical patients*</td>
<td>ELISA 3</td>
<td>RIBA 3</td>
<td>Moderate</td>
</tr>
<tr>
<td>India</td>
<td>Das et al, 2006</td>
<td>104</td>
<td>Unspecified</td>
<td>150</td>
<td>HIV negative outpatients</td>
<td>Unspecified</td>
<td>Unspecified</td>
<td>High</td>
</tr>
<tr>
<td>Iran</td>
<td>Ghaderi et al, 2007</td>
<td>73</td>
<td>Unclear</td>
<td>140</td>
<td>Blood donors</td>
<td>ELISA 3</td>
<td>RIBA 3</td>
<td>High</td>
</tr>
<tr>
<td>Israel</td>
<td>Yarom et al, 2007</td>
<td>62</td>
<td>62/62</td>
<td>62</td>
<td>Patients with other oral conditions*</td>
<td>ELISA 3</td>
<td>RIBA 3</td>
<td>Low</td>
</tr>
<tr>
<td>Brazil</td>
<td>Carrozzo et al, 1996</td>
<td>70</td>
<td>70/70</td>
<td>70</td>
<td>Patients with other oral conditions*</td>
<td>ELISA 2</td>
<td>RIBA 2</td>
<td>Low</td>
</tr>
<tr>
<td>Mexico</td>
<td>Luis-Montoya et al, 2005</td>
<td>36</td>
<td>Unspecified</td>
<td>60</td>
<td>Blood donors</td>
<td>ELISA 3</td>
<td>Unspecified</td>
<td>High</td>
</tr>
<tr>
<td>Japan</td>
<td>Tanei et al, 1995</td>
<td>45</td>
<td>37/45</td>
<td>45</td>
<td>Surgical patients (orthopedic)</td>
<td>ELISA 2</td>
<td>RIBA 2</td>
<td>Moderate</td>
</tr>
<tr>
<td>Nepal</td>
<td>Garg et al, 2002</td>
<td>86</td>
<td>29/86</td>
<td>43</td>
<td>Unknown</td>
<td>ELISA 2</td>
<td>Unspecified</td>
<td>Moderate</td>
</tr>
<tr>
<td>Nigeria</td>
<td>Daramola et al, 2002</td>
<td>57</td>
<td>Unspecified</td>
<td>48</td>
<td>Healthy and dermatology patients</td>
<td>ELISA 3</td>
<td>–e</td>
<td>Moderate</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>Ali et al, 2007</td>
<td>40</td>
<td>40/40</td>
<td>40</td>
<td>Dental patients</td>
<td>ELISA 3</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Serbia</td>
<td>Bokor-Bratic et al, 2004</td>
<td>48</td>
<td>48/48</td>
<td>60</td>
<td>Dental patients</td>
<td>ELISA 4</td>
<td>–e</td>
<td>Low</td>
</tr>
<tr>
<td>Spain</td>
<td>Santander et al, 1994</td>
<td>50</td>
<td>Unspecified</td>
<td>27</td>
<td>Dermatology patients</td>
<td>ELISA 2</td>
<td>PCR</td>
<td>High</td>
</tr>
<tr>
<td>Spain</td>
<td>Gimenez-Arnau et al, 1995</td>
<td>25</td>
<td>Unspecified</td>
<td>18</td>
<td>Unknown</td>
<td>Unspecified</td>
<td>Unspecified</td>
<td>High</td>
</tr>
<tr>
<td>Spain</td>
<td>Sanchez Perez et al, 1996</td>
<td>78</td>
<td>56/78</td>
<td>82</td>
<td>Dermatology patients</td>
<td>ELISA 2</td>
<td>Unspecified</td>
<td>Low</td>
</tr>
<tr>
<td>Spain</td>
<td>Bagan et al, 1998</td>
<td>100</td>
<td>100/100</td>
<td>100</td>
<td>Healthy subjects</td>
<td>ELISA 2</td>
<td>RIBA 2</td>
<td>Moderate</td>
</tr>
<tr>
<td>Spain</td>
<td>Gimenez-Garcia et al, 2003</td>
<td>101</td>
<td>53/101</td>
<td>99</td>
<td>Dermatology patients</td>
<td>ELISA 2</td>
<td>RIBA 2</td>
<td>Low</td>
</tr>
<tr>
<td>Thailand</td>
<td>Klarnit et al, 2003</td>
<td>60</td>
<td>60/60</td>
<td>60</td>
<td>Dental health care workers</td>
<td>ELISA 3</td>
<td>–e</td>
<td>High</td>
</tr>
<tr>
<td>Turkey</td>
<td>Ilter et al, 1998</td>
<td>75</td>
<td>Unspecified</td>
<td>75</td>
<td>Dermatology patients</td>
<td>Unspecified</td>
<td>–e</td>
<td>Moderate</td>
</tr>
<tr>
<td>Turkey</td>
<td>Kirtak et al, 2000</td>
<td>73</td>
<td>27/73</td>
<td>73</td>
<td>Dermatology patients</td>
<td>ELISA 3</td>
<td>Unspecified</td>
<td>Moderate</td>
</tr>
<tr>
<td>Turkey</td>
<td>Erkek et al, 2001</td>
<td>52</td>
<td>7/52</td>
<td>54</td>
<td>Dermatology patients</td>
<td>ELISA 3</td>
<td>Unspecified</td>
<td>Low</td>
</tr>
<tr>
<td>Turkey</td>
<td>Harman et al, 2004</td>
<td>128</td>
<td>52/128</td>
<td>128</td>
<td>Healthy subjects</td>
<td>ELISA 3</td>
<td>–e</td>
<td>Low</td>
</tr>
<tr>
<td>UK</td>
<td>Inagawa et al, 1998</td>
<td>55</td>
<td>55/55</td>
<td>110</td>
<td>Dental health care workers</td>
<td>ELISA 3</td>
<td>–e</td>
<td>High</td>
</tr>
<tr>
<td>USA</td>
<td>Tucko et al, 1999</td>
<td>45</td>
<td>13/45</td>
<td>32</td>
<td>Dermatology patients</td>
<td>ELISA 2</td>
<td>RIBA 2</td>
<td>Moderate</td>
</tr>
<tr>
<td>USA</td>
<td>Bellman et al, 1995</td>
<td>30</td>
<td>Unspecified</td>
<td>41</td>
<td>Dermatology patients</td>
<td>Unspecified</td>
<td>Unspecified</td>
<td>High</td>
</tr>
<tr>
<td>USA</td>
<td>Beaird et al, 2001</td>
<td>24</td>
<td>Unspecified</td>
<td>20</td>
<td>Dermatology patients (psoriasis)</td>
<td>Unspecified</td>
<td>Unspecified</td>
<td>High</td>
</tr>
</tbody>
</table>

Meta-analysis. The total number of patients of the included studies was 5404. In five studies no seropositive patients were found in either group. In these studies OR could not be calculated. The proportion of HCV-positive subjects was higher in the lichen planus group compared with controls in all the other studies but two, the OR of HCV seropositivity in patients with LP varying between 0.23 (95% CI: 0.01–5.85) and 15.94 (95% CI: 2.00–127.22). The summary estimate OR for all studies was 4.85 (95% CI: 3.58–6.56) (Figure 2), showing a statistically significant difference in the proportion of HCV seropositive subjects among lichen planus patients, compared with controls. Interestingly, despite the high geographical variety, heterogeneity of the results was not significant ($I^2 = 10.7\%$).

Subgroup analysis. In 11 studies all patients included had oral lesions (with and without cutaneous lesions), also in this subgroup, HCV seroprevalence was significantly more common among LP patients than controls (OR = 5.56 95% CI: 3.50–8.81). The summary estimate OR increased considerably in the Mediterranean studies (OR = 6.99 95% CI: 4.92–9.94), while, in the studies from Northern Europe, halved, becoming not significant (OR = 2.14 95% CI: 0.59–7.69). The sum-
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Oral Diseases

Sensitivity test and publication bias

Global one (4.76; 95% CI: 3.07–7.41). Further to the screening one, the OR was close to the considered studies including a confirmatory HCV test (3.91; 95% CI: 2.17–7.04) (Figure 3). Similarly, when we considered studies including a confirmatory HCV test further to the screening one, the OR was close to the global one (4.76; 95% CI: 3.07–7.41).

Characteristics of the included studies

The main characteristics of the 6 included studies are presented in Table 3. Two studies were from Brazil, and one each from France, Poland, Spain and Turkey. The control group was enrolled among dental patients in 3 studies, in two cases among healthy subjects and in one case among HCV-, HBV- and HIV- liver disease patients. In all studies HCV status was detected by ELISA and then confirmed by PCR or RIBA.

Critical appraisal of the included studies

On the basis of the criteria previously described, two studies resulted at low risk of bias, two were judged at moderate risk of bias, and two at high risk of bias. Only two studies clearly stated that the study group was formed by consecutive patients (Table 3).

Meta-analysis

The total number of patients of the included studies was 2197. In all six studies the prevalence of LP was higher among HCV-positive subjects compared with controls, the OR varying between 1.42 (95% CI: 0.13–15.94) and 7.43 (95% CI: 2.36–23.42). The summary estimate OR for all studies was 4.47 (95% CI: 1.84–10.86) (Figure 6), showing a statistically significant difference in the proportion of LP prevalence of LP among HCV-positive subjects, compared with controls. As for the previous analysis, despite high geographical variety, heterogeneity of the results was not significant (I^2 = 0%).

Only three out of six studies (Bagan et al, 1998; Figueiredo et al, 2002; Cunha et al, 2005) reported detailed data on anti-HCV treatments. In 2 studies

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Lichen planus</th>
<th>Controls</th>
<th>Odds ratio</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>All 2007</td>
<td>40</td>
<td>40</td>
<td>1.7%</td>
<td>3.90 [2.17, 7.04]</td>
</tr>
<tr>
<td>Garg 2002</td>
<td>64</td>
<td>43</td>
<td>1.7%</td>
<td>3.91 [2.17, 7.04]</td>
</tr>
<tr>
<td>Fillter 1998</td>
<td>75</td>
<td>75</td>
<td>2.0%</td>
<td>3.91 [2.17, 7.04]</td>
</tr>
<tr>
<td>Ingadu 1998</td>
<td>110</td>
<td>110</td>
<td>3.6%</td>
<td>3.91 [2.17, 7.04]</td>
</tr>
<tr>
<td>Bokor Bratic 2004</td>
<td>48</td>
<td>60</td>
<td>1.7%</td>
<td>3.91 [2.17, 7.04]</td>
</tr>
<tr>
<td>Tucker 1999</td>
<td>57</td>
<td>68</td>
<td>2.0%</td>
<td>3.91 [2.17, 7.04]</td>
</tr>
<tr>
<td>Rahman 2005</td>
<td>66</td>
<td>40</td>
<td>1.7%</td>
<td>3.91 [2.17, 7.04]</td>
</tr>
<tr>
<td>Daramola 2002</td>
<td>57</td>
<td>68</td>
<td>1.7%</td>
<td>3.91 [2.17, 7.04]</td>
</tr>
<tr>
<td>Cribier 1994</td>
<td>23</td>
<td>35</td>
<td>1.7%</td>
<td>3.91 [2.17, 7.04]</td>
</tr>
<tr>
<td>Dupin 1996</td>
<td>81</td>
<td>136</td>
<td>2.3%</td>
<td>3.91 [2.17, 7.04]</td>
</tr>
<tr>
<td>Ibrahim 1999</td>
<td>31</td>
<td>36</td>
<td>1.7%</td>
<td>3.91 [2.17, 7.04]</td>
</tr>
<tr>
<td>Y arom 2007</td>
<td>150</td>
<td>199</td>
<td>2.0%</td>
<td>3.91 [2.17, 7.04]</td>
</tr>
<tr>
<td>Bokor Bratic 2004</td>
<td>17</td>
<td>20</td>
<td>1.7%</td>
<td>3.91 [2.17, 7.04]</td>
</tr>
<tr>
<td>Y arom 2007</td>
<td>199</td>
<td>256</td>
<td>2.0%</td>
<td>3.91 [2.17, 7.04]</td>
</tr>
<tr>
<td>Beaird 2001</td>
<td>256</td>
<td>320</td>
<td>2.0%</td>
<td>3.91 [2.17, 7.04]</td>
</tr>
<tr>
<td>Y arom 2007</td>
<td>320</td>
<td>384</td>
<td>2.0%</td>
<td>3.91 [2.17, 7.04]</td>
</tr>
<tr>
<td>Bokor Bratic 2004</td>
<td>20</td>
<td>25</td>
<td>1.7%</td>
<td>3.91 [2.17, 7.04]</td>
</tr>
<tr>
<td>Y arom 2007</td>
<td>256</td>
<td>320</td>
<td>2.0%</td>
<td>3.91 [2.17, 7.04]</td>
</tr>
<tr>
<td>Bokor Bratic 2004</td>
<td>20</td>
<td>25</td>
<td>1.7%</td>
<td>3.91 [2.17, 7.04]</td>
</tr>
<tr>
<td>Y arom 2007</td>
<td>320</td>
<td>384</td>
<td>2.0%</td>
<td>3.91 [2.17, 7.04]</td>
</tr>
</tbody>
</table>

Figure 2 Forest plot of odds ratio of HCV seropositivity (95% confidence intervals) in patients with lichen planus.
Figure 3 Subanalysis: forest plot of odds ratio of HCV seropositivity (and 95% confidence intervals) in patients with lichen planus, in studies that ruled out the possibility of drug-induced lichenoid reactions.

Figure 4 Sensitivity test: forest plot of odds ratio of HCV seropositivity (and 95% confidence intervals) in studies at low risk of bias.

The visual examination of the symmetry of the funnel plot did not suggest large publication bias.

Discussion

In this systematic review we firmly confirm the association between HCV infection and LP. According to the meta-analysis, the summary estimate of OR showed that LP patients have about a five fold higher risk than the controls of being HCV seropositive and the OR for exclusive OLP was not substantially different from the global one. Moreover, quite the same OR was found analysing the prevalence of LP among patients with CLD due to HCV infection. However, the data showed a marked study and geographical variability, with the relationship between HCV and LP being prevalent in Japan, Mediterranean countries and the USA. This figure explains the strong regional connotation of the association among LP and HCV infection that was observed mainly in Southern Europe where HCV is highly prevalent. Interestingly, a similar geographic variability has been demonstrated for other EHM linked to HCV infection, such as porphyria cutanea tarda, lymphoma and even mixed cryoglobulinemia (Gisbert et al, 2003; Dal and Franceschi, 2006; Cohen Tervaert et al, 2007).

Several factors could be potentially responsible for the observed variability in results. These may include misclassification of LP, the highly variable prevalence of HCV infection across the world, differences in the viral characteristics of HCV, differences in genetic
susceptibility to HCV-induced LP, variability in the studies design and biases.

To avoid misclassification of LP, we decided to include in the meta-analysis only studies in which the clinical diagnosis of LP was confirmed histologically. Some studies have shown variability in both interobserver and intraobserver reliability in the clinicopathological assessment mainly of OLP (van der Meij and van der Waal I, 2003). However, a histological confirmation of the clinical diagnosis is worldwide accepted as a gold-standard practice in both LP and OLP studies.

Several medications including IFN-α and ribavirin can trigger mucocutaneous lichenoid reactions (McCartan and McCreary, 1997; Berk et al., 2007). However, IFN-α has been reported to have also no influence (Pawlotsky et al., 1995b) or even to ameliorate LP (Doutre et al., 1992; Strumia et al., 1993; Hildebrand et al., 1995; Pedersen, 1998) both clinically and histologically (Nagao et al., 1999). If lichenoid drug reactions are misdiagnosed and included in the samples of those with LP, it would result in an overestimation of the association between LP and HCV. Only a minority of the studies included in the meta-analysis stated clearly that a diagnosis of lichenoid reaction was excluded when they were analysed together a significant increased risk of being HCV-seropositive in LP patients was still found. Regarding specifically the anti-HCV treatment, while in some HCV-infected patients the lichenoid lesions could be secondary to anti-HCV therapy (Giuliani et al., 2007), it is unlikely that in the majority of the published studies most of the patients were exposed to antiviral treatments. Significantly, in the largest published study on EHM in HCV-infected patients (not included in the meta-analysis because the clinical diagnosis was not histologically confirmed in all the patients) showing a significant association between LP and HCV infection (El-Serag et al., 2002), less than 5% of 32,204 studied patients received antiviral therapies. In another study (Bagan et al., 1998), no significant differences in the frequency of OLP were observed between patients who received interferon-alpha (IFN-α) and those who did not.

Even if this meta-analysis highlighted a significant difference between Northern and Southern Europe, the pooled data from African studies with the highest HCV prevalence in the general population did not show a significant association (Ibrahim et al., 1999; Daramola et al., 2002). This suggests that any LP-HCV association

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**Table 3** Characteristics of the studies included in the meta-analysis investigating lichen planus prevalence in HCV positive patients

<table>
<thead>
<tr>
<th>Country</th>
<th>Reference</th>
<th>n</th>
<th>Characteristics</th>
<th>Screening</th>
<th>Confirmatory</th>
<th>HCV subjects</th>
<th>Controls</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>Figueiredo et al., 2002</td>
<td>126</td>
<td>Consecutive patients with HCV diagnosis</td>
<td>ELISA 2</td>
<td>RNA</td>
<td>898</td>
<td>Dental patients</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Cunha et al., 2005</td>
<td>134</td>
<td>Patients with other viral hepatitis were excluded</td>
<td>ELISA 3</td>
<td>RNA</td>
<td>95</td>
<td>Dental patients</td>
<td>Moderate</td>
</tr>
<tr>
<td>France</td>
<td>Cribier et al., 1998</td>
<td>81</td>
<td>HIV and HBV DNA excluded</td>
<td>ELISA 3</td>
<td>RNA</td>
<td>50</td>
<td>HCV-, HBV- and HIV- liver disease patients</td>
<td>Low</td>
</tr>
<tr>
<td>Poland</td>
<td>Sulka et al., 2006</td>
<td>39</td>
<td>23 chronic hepatitis and 16 chironis</td>
<td>ELISA a</td>
<td>RIBA a</td>
<td>29</td>
<td>Dental patients</td>
<td>High</td>
</tr>
<tr>
<td>Spain</td>
<td>Bagan et al., 1998</td>
<td>505</td>
<td>From Hepatology Unit Co-existent liver disease and treatment with antiviral or immunomodulatory agents were excluded</td>
<td>ELISA a</td>
<td>RIBA a</td>
<td>100</td>
<td>Healthy controls</td>
<td>High</td>
</tr>
<tr>
<td>Turkey</td>
<td>Dervis and Serez, 2005</td>
<td>70</td>
<td>Co-existent liver disease and treatment with antiviral or immunomodulatory agents were excluded</td>
<td>ELISA a</td>
<td>RNA a</td>
<td>70</td>
<td>Healthy controls</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

aNot otherwise specified.

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**Figure 6** Forest plot of odds ratio of lichen planus prevalence (and 95% confidence intervals) in HCV seropositive patients
cannot be only explained on the basis of HCV endemicity. Indeed, the studies investigating the frequency of LP among HCV-positive subjects showed prevalences generally higher than expected, independently of the geographical origin.

Viral factors (such as genotype or viral load) seem to be ruled out by the observation that LP can be associated world-wide with the same genotypes commonly found in patients without LP (Pawlotsky et al., 1995a; Lodi et al., 1997), though mainly genotype 1b seems associated with LP, and it could be uncommon in the UK (Harris et al., 1999).

Genetic differences among different populations should be also taken into account. HCV-related OLP appears associated mainly with the HLA-DR6 allele in Italy (Carrozzo et al., 2001) whereas it does not in UK (Carrozzo et al., 2005). However, a comparison study of the OLP-positive/HCV-positive group with an OLP-negative/HCV-positive group is necessary to ultimately test this plausible hypothesis.

Some controversial data could have been caused by the small cohort size in a number of studies. Indeed, the majority of the studies included less than 100 subjects. As a result some studies, mainly coming from countries with low prevalence of HCV infection (Ilter et al., 1998; Ingafou et al., 1998; Garg et al., 2002; Bokor-Bratic, 2004; Laeijendecker et al., 2005; Ali and Suresh, 2007), showed the lack of any case or control positive to HCV serology. In those cases, the key question is whether the power of such studies was sufficient to detect any difference in the prevalence of HCV. For example, in one of the above studies, performed in Netherlands (Laeijendecker et al., 2005), 100 patients with OLP and 100 controls were recruited. Considering a prevalence of HCV infection in Netherlands of 0.5% (Van der Poel et al., 2005), the power of such a study is only 20% (with an alpha error of 0.05, two tales). To obtain an acceptable power of 80%, more than 400 patients and 400 controls should have been recruited.

Age is a possible confounder because, in many populations, the prevalence of HCV exposure varies in different age groups (Alter, 2007), and older individuals have a higher prevalence of LP. However, the meta-analysis seems to confute the hypothesis that the high frequency of HCV seropositivity found in LP groups is caused by the increased prevalence of HCV infection in elderly patients (Campisi et al., 2004). Indeed, the subgroup analysis of studies with LP patients ≤50 years still showed a significant association with HCV infection.

Given the design of most of the case-control and cohort studies published, it is impossible to establish whether the HCV exposure occurred before or after the onset of LP. As a result, HCV-infected patients might have an increased risk of developing LP or conversely, patients with LP could have an enhanced risk of HCV infection. A very recent epidemiologic study from Japan suggests that OLP prevalence in HCV-infected patients increased significantly as the subjects grew older (Nagao et al., 2007) suggesting that the patients are very likely first infected with HCV and only later develop LP. This prospective study suggests also that the duration of the infection should be a potential source of heterogeneity in the published studies. Moreover, in countries where the prevalence among the LP-free subjects is low, the spread of the virus might be recent and not yet produced full consequences on LP development. Thus, in countries with a very low prevalence of HCV, LP should be probably better identified in HCV-infected patients rather than seeking to find HCV infection in LP patients (Carrozzo, 2001). Notably, in this meta-analysis we could not include any study looking for LP in chronic HCV infected from countries with low HCV prevalence. It has to be considered, however, that such a study could possibly require the recruitment of a large number of patients for being significant making it very difficult on a practical base and possibly clinically negligible.

Clinical implications of the results presented in this systematic review are particularly relevant. A high proportion of patients affected by HCV-associated chronic hepatitis may have persistently normal aminotransferase levels and recent data suggest that only a minority of people with HCV in Europe are aware of their infection (Merkinaite et al., 2008), thus testing for HCV patients with LP can lead to the diagnosis of a condition for which treatments are available and precautions can be useful to avoid further spread. Moreover, because chronic HCV infection can lead to cirrhosis and hepatocellular carcinoma (Eisen et al., 2005; Alter, 2007) and OLP is a potentially malignant disorder, an early diagnosis and a proper management might save lives and being beneficial in reducing health care costs.

In conclusion, this systematic review and meta-analysis shows that LP may be significantly associated with HCV infection mainly in Mediterranean countries, in Japan and USA. All the sub-analyses and the sensitivity assessments done strongly and consistently suggest this possible association. Because the HCV can replicate in the skin and in the oral mucosa and HCV-specific T cells have been found in OLP specimen (Carrozzo et al., 2002; Pilli et al., 2002), the virus could be involved in the pathogenesis of at least some OLP cases, probably via an immunological pathway still to be defined.

Finally, some of the controversial epidemiological data published could have been influenced by methodological biases (such as misclassification of the disease, small sample size, and recent acquisition of HCV, etc.) further to a generic geographic effect linked to worldwide HCV prevalence.

References


