The Relationship Between Lichen Planus and Hepatitis C Clarified

LOOKING AT THE LITERATURE ABOUT THE association of lichen planus (LP) and hepatitis C virus (HCV) infection brings to mind the parable about blind men examining different parts of an elephant and coming to different conclusions about its appearance. Using meta-analysis of well-selected case-control studies, Shengyuan et al[1] provide a complete picture. From their analysis of the data, they conclude that the association exists in some regions (eg, East and Southeast Asia, South America, the Middle East, and Europe) but not in others (eg, North America, South Asia, and Africa).

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The point estimate of the summary odds ratio (OR) of the prevalence of HCV exposure in patients with LP and controls was 5.4 (95% confidence interval [CI], 3.5 to 8.3). The positive association was statistically significant and statistically homogeneous among studies from East and Southeast Asia and South America. The positive association was statistically significant and statistically heterogeneous among studies from the Middle East and Europe. The point estimate of the OR for association was also positive for studies from South Asia, North America, and Africa, but the results were not statistically significant at the $P = .05$ level (**Table**).[2-4]

In all regions where the results were not statistically significant the data were heavily skewed toward a positive association (**Figure**). In fact, if one uses the appropriate control group (ie, randomly selected patients with psoriasis seen in the same institution) in the study by Chuang et al,[5] the OR of the meta-analysis of the studies of the prevalence of HCV exposure in patients with LP compared with controls identified as being from North America was 3.8 (95% CI, 1.6 to 8.9; $P = .003$) (Figure).[1,5] The comparable figures for studies from Africa were OR, 11.6 (95% CI, 0.8 to 172; $P = .07$). In interpreting results for which the point estimate shows a positive effect and the confidence is highly skewed toward a positive effect but crosses the null, Pocock and Ware[6] suggest that such studies be interpreted as weak evidence of an effect or association. There were only 2 studies from South Asia. They included a total of 359 individuals in the LP and control groups, and the only 4 with HCV were in the LP group (Figure). The point estimate of the OR of the meta-analysis of these 2 studies is 155, and the 95% CI is so wide that the meta-analysis cannot exclude an OR of 10^8. The meta-analysis of the studies from South Asia is thus underpowered to detect a meaningful difference in prevalence. Thus, one can conclude from the data of Shengyuan et al[1] that epidemiological studies indicate that HCV exposure is more prevalent in patients with LP than in control populations. This association seems to be the case in all regions of the world.

However, epidemiological studies do not and cannot prove that HCV infection and LP are causally related. External evidence and biologic plausibility are also needed to reach this conclusion. There is no evidence, to my knowledge, and it is not biologically plausible, that patients with LP are more susceptible to HCV infection.

The alternative possibility, that HCV infection precedes, causes, or is involved in the development or pathogenesis of LP, is much more intriguing.[7] Hepatitis C vi-

Table. Estimated Prevalence of Hepatitis C Virus (HCV) in Patients With Lichen Planus (LP) in Different Geographic Regions

Region	OR of Prevalence of HCV in Patients With LP vs Controls (95% CI)	Prevalence of HCV in Population, %[a]	RR of HCV in Patients With LP vs Controls[b]	Estimated Prevalence of HCV in Patients With LP (Column 3 × Column 4), %
East and Southeast Asia	4.7 (3.1 to 7.2)	2.2	4.3	9.5
South America	6.3 (3.1 to 12.8)	1.7[c]	5.8	9.9
South Asia	4.0 (0.5 to 34.5)	2.2	3.8	8.4
Middle East	6.4 (2.7 to 15)	4.6	5.1	23.5
Europe	4.3 (2.5 to 7.1)	1.0	4.2	4.2
Africa	3.6 (0.6 to 20.3)	5.3	3.2	17.0
North America[d]	3.8 (1.6 to 8.9)	1.7[c]	3.6	6.1
Overall	5.4 (3.5 to 8.3)	3.1	4.8	14.9

Abbreviations: CI, confidence interval; OR, odds ratio; RR, relative risk.
[a] See the World Health Organization fact sheet[2] and "Global prevalence of hepatitis A, B, and C Weekly Epidemiological Record."[3]
[b] See study by Zhang and Yu.[4]
[c] Data provided for "the Americas."
[d] My calculation using the appropriate control group (ie, randomly selected patients with psoriasis seen in the same institution) in the study by Chuang et al.[5]

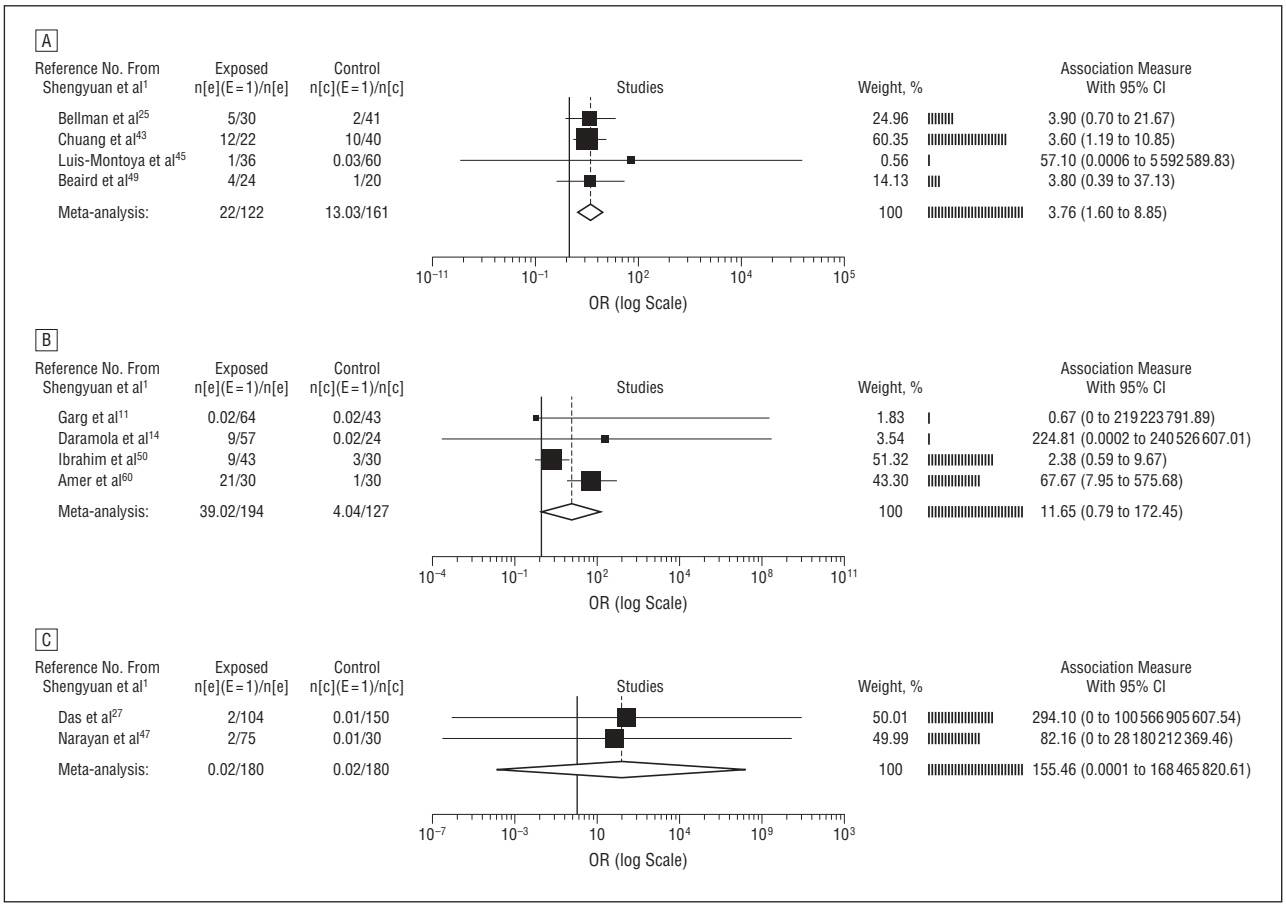

Figure. Meta-analysis performed with MIX software (version 1.7).[17,18] A, North America; B, Africa; C, South Asia. CI indicates confidence interval; OR, odds ratio. The numerators are the numbers of patients with hepatitis C virus detected; the denominator, the total studied; "exposed" refers to patients with lichen planus; and "control" is the control group.

rus is not known or suspected to infect epidermal cells, although several groups have reported detecting HCV RNA in epithelial cells in patients with HCV.[8-10] Erkek et al[8] found HCV RNA by polymerase chain reaction (PCR) in the serum and lesional skin biopsy specimens in 5 of 7 patients with HCV and LP. Hepatitis C virus RNA was found in only 1 of 4 nonlesional skin biopsy specimens in the 4 patients who agreed to have nonlesional skin biopsies. Arrieta et al[9] found positive hybridization signals using in situ hybridization in cells randomly distributed in the basal layer of oral mucosal biopsy specimens from patients with HCV in the serum whether they had LP or not. Almost all of the cells had positive-strand and negative-strand HCV RNA, which they concluded demonstrated HCV replicates in epithelial cells of patients with HCV. However, infected cells were not associated with lichenoid inflammation.

In contrast, Harden et al[11] found no HCV transcripts by reverse-transcriptase PCR in biopsy specimens from 5 patients who had LP and HCV. Furthermore, the response of LP to treatment of HCV with interferon with or without ribavirin has been inconsistent, lending evidence neither for nor against the role of HCV in the pathogenesis of LP.[11,12]

There is some evidence that LP is an autoimmune disease mediated by T cells and directed at autologous keratinocytes.[13] We have shown that cytotoxic T-cell lines and clones derived from lesional skin of patients with LP lyse autologous lesional keratinocytes more readily than T-cell lines and clones derived from nonlesional skin.[14] Pilli et al[15] found HCV-specific $CD4^+$ and $CD8^+$ T cells more readily in oral lesional biopsy specimens than in peripheral blood in patients with LP and with HCV infection. It is intriguing to speculate that passively or actively acquired HCV antigens interacting with keratinocytes may trigger an autoimmune reaction that results in LP.[7,13]

If one accepts the conclusion that the prevalence of HCV is higher in patients with LP than in the normal population, should patients with LP be screened for HCV? For screening to be worthwhile, we would need evidence that we will detect HCV in patients with LP who have previously undiagnosed HCV *and* that the knowledge gained would prevent the spread of HCV or improve the health of the patients with LP who have HCV detected by the screening.[16]

The major sources of spread of HCV are sharing needles with infected intravenous (IV) drug users and transfusion with unscreened blood products. Having sex with infected intravenous drug users is also a risk factor. These behaviors may be alterable.

Because only 20% to 30% of HCV-infected individuals develop clinically evident acute hepatitis, it is likely that at least some patients with LP are unaware that they have HCV.[2,3,16] Chronic HCV infection can lead to cir-

rhosis and hepatocellular carcinoma. Combined treatment with interferon and ribavirin is effective in 30% to 50% of patients but is very expensive.

Given the ORs and prevalence figures in different regions of the world (Table), we would expect that the prevalence of HCV in patients with LP to vary from 4% in Europe to 24% in the Middle East.[2-4] However, the percentage of patients with LP who have undiagnosed HCV that will be initially detected by screening is unknown. Therefore, the prevalence of newly discovered HCV infections in patients with LP may be lower. Lapane et al[16] have suggested that screening is cost-effective when the prevalence of HCV is greater than 7%.

As outlined by Lapane et al,[16] identifying individuals with HCV infection may decrease transmission by eradicating viremia with treatment and possibly by educating patients about the disease and about ways to curtail behaviors that promote transmission (eg, unprotected sex or sharing needles). Early diagnosis and treatment may save lives and are beneficial in reducing health care costs. It also affords individuals with HCV infection the opportunity to avoid other hepatotoxins (eg, alcohol).

Potential forms of screening include taking a history for risk factors for HCV (eg, IV drug use, sex with IV drug users, or history of blood transfusion), serum enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase), or serologic testing. Lapane et al[16] found that determining a patient's risk based on answers to identified risk factors (IV drug use, sex with IV drug users, history of blood transfusion, male sex, and age of 30-49 years) and testing those with a risk greater than 7% (based on a logistic regression model) with an enzyme-linked immunosorbent assay (ELISA) for anti-HCV antibodies was an optimal strategy. It would detect 4.4 cases per 100 individuals screened at a cost of $357 per case detected. Limiting screening to individuals with 1 "socially intrusive" risk factor (IV drug use or sex with IV drug users) or 2 or more "non–socially nonintrusive" risk factors (history of blood transfusion, male sex, and age of 30-49 years) would detect 4.6 cases per 100 individuals screened at a slightly larger cost, $439 per case detected. Screening everyone with ALT would be prohibitively expensive ($1047 per case detected) and not cost-effective.[16]

The work of Shengyuan et al[1] is an important contribution to the discourse about LP and HCV. It should stimulate further discussion and research to address the question of screening of patients with LP for HCV. From a practical standpoint, it would be prudent to at least ask patients seen with LP whether they have major (IV drug use or sex with IV drug users) or minor (history of blood transfusion, male sex, and age of 30-49) risk factors for having HCV and to screen those with clinically significant risk with an ELISA for HCV antibodies.

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