

Localization of Hepatitis C Virus in Gastrointestinal Mucosa: A Possible Reservoir for Relapse

To the Editor:

Hepatitis C virus (HCV) is able to infect different extrahepatic sites such as peripheral blood mononuclear cells (PBMCs), renal cells, thyroid cells, gastric cells, and there is mounting evidence that these could represent replicative compartments for the virus.^{1,2} Moreover, HCV seems to be involved in development of B-cell non-Hodgkin's lymphoma of the gastric mucosa.³⁻⁵ Treating patients with HCV infection and facing day by day the clinical problem of relapse after treatment, we analyzed HCV gastric localization from a different point of view. In 23 patients we compared viremia with the status of HCV in gastric biopsy specimens and PBMCs. Samples were collected when patients underwent upper gastrointestinal endoscopy for dyspeptic symptoms. The method we used to detect HCV RNA on tissue was a homemade reverse-transcription polymerase chain reaction with primers at the 5'-untranslated region and extraction of viral RNA was made by a phenol-guanidine isothiocyanate medium (TRIzol; Life Technologies, Grand Island, NY).⁶ We found all 15 patients with positive viremia (HCV-RNA at Cobas Amplicor v2.0; Roche Diagnostic System, Basel, Switzerland) to be positive for the presence of HCV on tissue and PBMCs; in 2 patients, HCV RNA was positive on serum, negative at biopsy but their PBMCs were infected. No apparent correlation was observed between viral load and HCV presence in gastric mucosa. Two patients with negative viremia and PBMCs after antiviral treatment were positive for HCV RNA on gastric sample and eventually relapsed (after 6 and 18 weeks) (Table 1).

We suggest that the gastrointestinal compartment is involved in virologic relapse after viral clearance, being a reservoir for the virus and a possible source of re-infection for hepatocytes through portal vein blood. The gastrointestinal tract is an interesting compartment for HCV localization; the turnover of gastrointestinal cells is extremely high and this could account for replication of HCV and cell death without consequent inflammation. The finding of a positive hidden compartment for HCV and simultaneous negative viremia is not new, as McHutchinson et al.⁷ already showed the possibility of an infected liver without detectable viremia. If replication in gastrointestinal cells exists, this could represent a continuous new source of viral particles for the liver, determining re-infection of hepatocytes. Results of antiviral treatment for HCV chronic hepatitis have improved to more than 50% of sustained virologic response.⁸ The challenge for the future of chronic HCV infection is still prevention of clinical relapse after treatment or after orthotopic liver transplantation, and a better understand-

ing of HCV tropism and sites of infection could help find new therapeutic targets and strategies.

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References

1. Yan FM, Chen AS, Hao F, et al. Hepatitis C virus may infect extrahepatic tissues in patients with hepatitis C. *World J Gastroenterol* 2000;6:805-811.
2. Carrozzo M, Quadri R, Latorre P, et al. Molecular evidence that the hepatitis C virus replicates in the oral mucosa. *J Hepatol* 2002;37:364-369.
3. Tursi A, Brandimante G, Chiarelli F, et al. Detection of HCV RNA in gastric mucosa-associated lymphoid tissue by in situ hybridization: evidence of a new extrahepatic localization of HCV with increased risk of gastric malt lymphoma. *Am J Gastroenterol* 2002;9:1802-1806.
4. De Vita S, De Re V, Sansonno D, et al. Gastric mucosa as an additional extrahepatic localization of hepatitis C virus: viral detection in gastric low-grade lymphoma associated with autoimmune disease and in chronic gastritis. *HEPATOLOGY* 2000;3:182-189.
5. Cammarota G, Cianci R, Grillo RL, et al. Relationship between gastric localization of hepatitis C virus and mucosa-associated lymphoid tissue in *Helicobacter pylori* infection. *Scand J Gastroenterol* 2002;10:1126-1132.
6. Garson JA, Ring C, Tuke P, et al. Enhanced detection by PCR of hepatitis C virus RNA. *Lancet* 1990;336:878-879.
7. McHutchinson JG, Poynard T, Esteban-Mur R, et al. Hepatic HCV RNA before and after treatment with interferon alone or combined with ribavirin. *HEPATOLOGY* 2002;35:688-693.
8. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002;347:975-982.

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doi:10.1053/jhep.2003.50322

Table 1. Presence of HCV RNA in Gastrointestinal Mucosa With Respect to Viremia and PBMC Status

Total (n = 23)	HCV Positive (n = 17)		HCV Negative (n = 6)	
	PBMC Positive	PBMC Negative	PBMC Positive	PBMC Negative
BIO positive (n = 17)	15	0	0	2
BIO negative (n = 6)	2	0	0	4

NOTE. Fifteen of 17 patients (88%) with positive viremia were HCV-RNA positive on tissue examination, whereas 2 patients with negative RNA on serum after combined antiviral treatment (IFN + ribavirin) were positive on gastric biopsy.