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eViralHepatitis Review
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HEPATITIS C AND HOST GENETICS

In this Issue...

The impact of human genetics on the course of infectious diseases is demonstrated by examples of variation that are relevant for responses to acute infection and pharmacologic therapy in patients with hepatitis C. In recent years, host genetics have been increasingly appreciated as major factors that contribute to the distinct clinical outcomes observed in a number of infectious diseases, both during their natural course as well as during therapy. Hepatitis C is particularly informative in this regard, since the determinants of the striking interindividual differences in distinct outcomes (eg, steatosis and fibrosis), spontaneous clearance, response to therapy, and side effects of treatment have not been well understood in the past. All of these factors have been greatly elucidated by recent studies that emphasize the important role played by host genetic background.

Several examples of the influence of human genetic variation on the course of or susceptibility to infectious diseases have been recognized for some time, including alleles that encode genes responsible for red blood cell abnormalities that may protect against malaria (eg, sickle cell trait and glucose-6-phosphate dehydrogenase deficiency). Many of these variations have been characterized by an overt phenotype and Mendelian inheritance. Recent developments, however, have enabled us to identify genetic variants that have a more subtle impact or may become relevant only during therapy. Genome-wide association studies allow for a comprehensive, unbiased investigation of genotype-phenotype relationships.

In this issue, we review recent investigations into the genetic predictors of therapeutic response, genetic variants that may determine ribavirin-induced anemia, the role played by *IL28B* in sustained virologic response, and the influence of single-nucleotide polymorphisms in chronic liver disease.

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Explain the potential for host genetic factors to cause interindividual effects on the course of infectious disease in general and on hepatitis C in particular
- Identify the likely cause of ribavirin-induced anemia as reported among some patients with hepatitis C
- Discuss the impact of *IL28B*-associated genetic variation on response to both interferon (IFN)-based and IFN-free therapy

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January 31, 2012; activities expire 2 years from the date of publication.

STATEMENT OF NEED;

Central ideas emerged from our needs assessment. In order to provide optimal treatment to patients with viral hepatitis:

- Clinicians do not effectively identify their patients at risk for, or infected with, HBV
- Clinicians lack the ability to interpret positive HBV screening and do not adequately counsel their patients re: their HBV status (for treatment or vaccination)
- Clinicians do not properly treat, monitor, or refer their patients with viral hepatitis and moreover, they lack awareness of current treatments and emerging research

INTENDED AUDIENCE

This activity has been developed for hepatologists, primary care physicians, infectious disease specialists, nurses, nurse practitioners, and others involved in the care of patients with viral hepatitis.

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- Clinicians require more evidence on tailoring HCV treatments to manage treatment side effects more effectively
- Clinicians require more evidence-based information to manage antiviral treatment more effectively in co-infected patients

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THIS ISSUE

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COMMENTARY

More than 40 human genes have been described as modulators of response and adverse events in the treatment of hepatitis C[1]. These genes are involved in inflammatory, immune, and antiviral pathways. Examples are the human leukocyte antigen (HLA) genes tumor necrosis factor-*αTNF*-α) and interleukin *(IL)-10*. In recent years, novel techniques, along with increased precision and depth in genomic research, have enabled us to detect even subtle genetic effects modifying disease outcomes that may become apparent only in large cohorts of patients. A recent major breakthrough was the finding that variation in the region of *IL28B*—the gene coding for the IL28B protein, also known as interferon (IFN)-λ3—is highly predictive of response to treatment with peginterferon (Peg-IFN)-α and ribavirin (RBV) in patients with chronic hepatitis C (CHC).[2-4] Subsequent work has also confirmed an association between the host *IL28B* genotype and spontaneous viral clearance.[5,6] In addition, this genetic polymorphism was shown to be at least partially responsible for previously unexplained ethnic differences in response rates to chronic HCV therapy. Ge and colleagues estimate that the *IL28B*-related single-nucleotide polymorphism (SNP) rs12979860 accounts for > 50% of the variability between responses to Peg-IFN/RBV treatment among African Americans and Caucasians.[2] This unexpected association quickly became a central theme in hepatitis C research. A PubMed search for "IL28B" and "hepatitis C" in September 2012 yielded > 380 publications since 2009. Moreover, patient stratification according to *IL28B* genotype has become standard practice for hepatitis C clinical trials, including those that do not incorporate Peg-IFN. Despite very solid statistical evidence for this association, its biological underpinning is unknown; current knowledge remains descriptive in the absence of experimental data to support a mechanistic explanation.

Although *IL28B* genotyping has been adopted by some clinicians in certain situations, common standards for testing are currently lacking. Moreover, whereas the *IL28B* genotype was shown to account for the majority of treatment response rates in patients with chronic hepatitis C, the predictive value in the wake of current therapeutic trends would appear to be insufficiently robust to justify widespread clinical use. Therefore, genotyping has not become common practice and has not widely influenced individual treatment decisions. However, Suppiah and colleagues (reviewed in this issue) demonstrate the possibility of combinations of genotypes being used to strengthen the pretreatment predictive value for treatment outcomes.

Direct-acting antiviral agents (DAAs) against HCV recently have been developed, with two of them (telaprevir and boceprevir) approved by the US Food and Drug Administration in May 2011 for the treatment of genotype 1 chronic hepatitis C. Initially, it was unclear whether the considerable effect of the *IL28B* genotype demonstrated both for spontaneous clearance and for response to Peg-IFN/RBV therapy in many studies would still play a role in these novel treatment regimens. Although the new standard therapy for genotype 1 CHC has been welcomed by clinicians and patients alike because of its significantly improved response rates, a major drawback remains its dependence on IFN, which is associated with an unfavorable side effect profile that excludes many patients from therapy in the first place and leads to a high rate of treatment discontinuation. Many promising DAAs are currently in clinical development, and very potent IFN-free combination regimens are under investigation, with response rates that surpass the previous standard of care and more tolerable side effect profiles. On first inspection, it would appear less clear that *IL28B* status could influence the success of regimens with direct antiviral effects. This may not be the case, however. For example, interim analysis of the SOUND-C2 study, presented by Zeuzem and collaborators (reviewed in this issue) at the 47th Annual Meeting of the European Association for the Study of the Liver in April 2012, provides evidence that the *IL28B* genotype indeed remains an important predictor of treatment success in an IFN-free regimen for genotype 1 hepatitis C. These findings support the continued relevance of the *IL28B* genotype and may reflect the role played by *IL28B* in the ultimate clearance events that precede a sustained virologic response (SVR).

Another example of a pharmacogenomic discovery relevant to the treatment of hepatitis C is genetic variation on chromosome 20, which was found to be highly predictive of RBV-induced hemolytic anemia by a genome-wide association study (GWAS). Fellay and coworkers (reviewed in this newsletter) were able to identify the association between anemia that develops in certain individuals undergoing RBV therapy and functional genetic variants that lead to deficiency in inosine triphosphatase (ITPA)—an enzyme that breaks down inosine triphosphate (ITP) in red blood cells (RBCs). ITPA deficiency turned out to be linked to the protective allele. RBV depletes adenosine triphosphate (ATP) in erythrocytes, thereby potentially causing hemolysis. ITP may be able to replace ATP unless it is itself broken down by ITPA. Hence, lack of ITPA may protect against hemolysis during RBV therapy, which would conveniently close the gap on the GWAS findings. Evidence for a similar regulatory mechanism underlying *IL28B*-related effects, however, is currently lacking. Despite concerted efforts, the causative SNP has not been pinpointed, nor have the responsible biological events been identified. This alludes to a more complex situation than with the ITPA example.

Clinical parameters, such as old age or male gender, have explained only a small portion of the considerable interindividual differences in quality and severity of liver injury that are observed in patients with HCV infection. As discussed in the review by Trépo and associates, a SNP in the *PNPLA3* gene seems to be strongly associated with steatosis and fibrosis, and may turn out to be a useful clinical predictor.

Novel scientific tools have enabled studies that have led to recent breakthroughs in research. Notably, genetic variation in the area of *IL28B* was identified as highly predictive of therapeutic response in patients with HCV infection. Further research is warranted to identify the causal mechanism for this association. Genetic studies have identified variants that cause ITPA deficiency as having a protective effect against RBV-induced anemia. These discoveries may help to individualize therapy and may serve as a paradigm for the application of pharmacogenomics in other diseases. A major question that remains, with ever-improving SVR rates reported with IFN-sparing DAA regimens, is whether the discriminatory value of pharmacogenomic markers may become confined to treatment subgroups with less-than-optimal outcomes.

Commentary References

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back to top

IMPROVING THE PREDICTION OF PATIENT RESPONSE TO HCV THERAPY

Suppiah V, Gaudieri S, Armstrong NJ, et al; International Hepatitis C Genetics Consortium (IHCGC). IL28B, HLA-C, and KIR variants additively predict response to therapy in chronic hepatitis C virus infection in a European cohort: a cross-sectional study. *PLoS Med.* 2011;8(9):e1001092.

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The *IL28B* genotype has been described as the single best predictor of response to hepatitis C therapy with Peg-IFN/RBV. It correctly predicts treatment failure, however, in only about two-thirds of cases. Variation in human leukocyte antigen gene C (*HLA-C*) and killer immunoglobulin-like receptor (*KIR*) genes are relevant to the control of HCV by the immune system. The authors of this study attempted to investigate whether genotyping of the regions for *HLA-C* and *KIR*, in addition to *IL28B*, improves the predictability of response to HCV therapy. This multicenter study comprised patients with genotype 1 chronic HCV infection, including 417 patients with an SVR upon receiving therapy, 493 who failed to achieve an SVR, and 234 with spontaneous clearance. In addition to *IL28B*, genotyping was performed for two *HLA-C* variants—C1 and C2—and several *KIR* genes. *HLA-C* variants have been shown to interact with certain *KIR* genes that are either inhibitory or activating, and to lead to differential activation of natural killer cells.

Patients homozygous for *HLC-C2* were more likely to fail to clear the virus on therapy than both *HLC-C1* homozygous and heterozygous individuals. Moreover, the *KIR* genotype per se was not found to predict spontaneous clearance or therapeutic response. The presence of *KIR2DL3* in conjunction with homozygosity for *HLC-C2*, however, increased the likelihood of therapeutic failure compared with other combinations. The predictive value for treatment failure increased from 66% with *IL28B* alone to 80% with combined *IL28B* and *HLA-C* genotyping.

The authors demonstrated that the predictive value of the IL28B genotype is substantially improved by additionally genotyping *HLA-C* and *KIR*. This finding underscores the crucial role of host genetics for treatment responses in patients with CHC. Although the relevance of the *IL28B* genotype was only recently discovered, it has already made its way into clinical practice and is used in certain situations to evaluate a patient's likelihood of achieving therapeutic success. Investigations to further clarify how genomic variation directs response to hepatitis C therapy, particularly in emerging novel IFN-sparing treatment regimens, are warranted. The value of genotyping in hepatitis C therapy in different settings and populations has to be further defined in order to facilitate the creation of standards for clinical use.

back to top

RBV-INDUCED ANEMIA

Fellay J, Thompson AJ, Ge D, et al. *ITPA* gene variants protect against Anemia in patients treated for chronic hepatitis C. *Nature.* 2010;464 (7287):405-408.

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With the use of a GWAS, the authors sought to identify genetic variants that may determine treatment-related anemia in patients receiving Peg-IFN/ RBV for chronic hepatitis C. Data from 1286 patients with genotype 1 chronic HCV infection were analyzed. The use of DNA chips for the GWAS enabled the investigators to evaluate the association

between each of 565,759 SNPs scattered across the genome (directly and indirectly covering most of the known genetic variation in man) and changes in hemoglobin (Hb) levels under treatment. Three phenotypes related to Hb changes between baseline and week 4 of therapy were considered: (1) absolute reduction in Hb, (2) reduction in Hb of > 3 g/dL, and (3) reduction in Hb levels to < 10 g/dL.

Several SNPs in a circumscribed region on chromosome 20 were found to be strongly associated with treatment-induced reduction in Hb levels at week 4. When looking for causal SNPs by searching the relevant region for functional variants, the authors demonstrated that protection from anemia is linked strongly to 2 variants that lead to deficiency of ITPA—a state known to cause accumulation of ITP in the erythrocyte and previously regarded as a benign red cell enzymopathy. One of these causal SNPs represents a missense mutation in exon 2 of *ITPA*, and the other is a splicing-altering intronic mutation. By using a regression model, these two variants were found to explain, in its entirety, the detected association signal. The strongest associations with anemia outside the *ITPA* region were detected in variants of the hexokinase 1 (*HK1*) gene, which is known to be involved in RBC homeostasis. These findings, however, did not reach genome-wide statistical significance ($P < 10^{-8}$).

The authors identified the likely causative genetic variants for anemia during Peg-IFN/RBV therapy. These variants are responsible for ITPA deficiency and thus result in ITP accumulation in RBCs. Since anemia is predominantly an adverse event associated with the use of RBV, this finding may still be relevant for novel treatments that continue to use RBV.

GWAS are powerful tools for identifying variants linked to certain phenotypes, particularly for previously unexpected associations, such as in the case of *ITPA*. Because of a large number of independent comparisons, the method requires a very strong level of statistical significance in order to minimize the risk for false-positive test results. A high statistical threshold, on the other hand, may lead investigators to miss biologically relevant associations in the data noise. In the current article, for example, *HK1* variants marginally failed to achieve genome-wide significance (lowest $P = 8.9 \times 10^{-7}$) and were therefore not regarded as true hits. *HK1* deficiency has repeatedly been described as a cause of severe anemia. Hence, it seems plausible that synergistic toxicity by RBV and *HK1* variants could be a cause of anemia in the treatment of hepatitis C.

back to top

ASSOCIATION OF *IL28B* GENOTYPE AND RESPONSE TO BOCEPREVIR THERAPY IN PATIENTS WITH HCV INFECTION

Poordad F, Bronowicki JP, Gordon SC, et al; SPRINT-2 and RESPOND-2 Investigators. Factors that predict response of patients with hepatitis C virus infection to boceprevir. *Gastroenterology*. 2012;143(3):608-618.e1-e5.

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The aim of the present study was to evaluate factors associated with an SVR in the treatment of CHC with boceprevir—one of the two protease inhibitors recently approved for the disorder. Both previously untreated patients (from the Serine Protease Inhibitor Therapy 2 [SPRINT-2] trial) and those who had failed to respond to therapy (from the Retreatment with HCV Serine Protease Inhibitor Boceprevir and PegIntron/ Rebetol 2 [RESPOND-2] trial) were evaluated. Treatment with Peg-IFN/RBV alone for 48 weeks was compared with treatment with Peg-IFN/RBV for 4 weeks followed by triple therapy with Peg-IFN/RBV/boceprevir for an additional 24 to 44 weeks.

HCV RNA level was determined at week 4 of Peg-IFN/RBV treatment (before the possible introduction of boceprevir) and was defined as a "good response" if it yielded a ≥ 1 $\log_{10}$ decrease. Good response has been shown to be predictive of SVR in both the SPRINT-2 and the RESPOND-2 studies. If HCV RNA levels were undetectable at week 8, treatment was shortened according to the protocol (referred to as response-guided therapy).

In the previously untreated patients (SPRINT-2), a low baseline viral load, a favorable *IL28B* genotype (rs12979860 CC vs non-CC genotype), the absence of cirrhosis, HCV subtype 1b, and non-black race were all predictive of SVR. If patients had failed to respond to treatment in the past (RESPOND-2), however, the only factor that was a significant predictor of SVR was previous relapse (vs nonresponse; odds ratio, 2.6).

Patients with a good response (defined as above) to IFN had substantially higher SVR rates in both studies. Baseline predictors of good response to IFN included *IL28B* genotype, low baseline viral load, absence of cirrhosis, and lower body mass index among the previously untreated patients. In those with a history of treatment failure, *IL28B* genotype and previous relapse vs nonresponse were both predictive of IFN response. In patient groups in both studies, the *IL28B* genotype exhibited a stronger association with good IFN response than did other baseline (pretreatment) factors. Early response to IFN, however, had an even better correlation with SVR than did *IL28B* genotype.

In both studies, 28% to 38% of patients with a poor IFN response (≤1 $\log_{10}$ decrease in HCV RNA level at week 4 of IFN treatment) achieved an SVR if treated with boceprevir, compared with 0% to 4% in the control arm. Boceprevir-treated patients with a poor response to IFN had significantly higher SVR rates if they were infected with HCV subtype 1b vs HCV subtype 1a (47% vs 25%, respectively).

Response-guided therapy was evaluated as well. *IL28B* genotype CC patients who received boceprevir had undetectable HCV RNA levels by week 8 and were therefore eligible for shortened treatment durations in 89% (SPRINT-2) and 76% (RESPOND-2), respectively. Lower rates were reported in genotype CT/genotype TT patients (53%/42% in SPRINT-2; 46%/42% in RESPOND-2).

Based on two previous trials in both treatment-naïve (SPRINT-2) patients, as well as in patients who failed previous therapy (RESPOND-2), the current paper describes factors that predict the likelihood of response to combination therapy with boceprevir. *IL28B* genotype predicts response to IFN at four weeks and may identify candidates for shorter duration of treatment. The results confirm the biological significance of the *IL28B* genotype in the setting of the recently approved standard therapy with a protease inhibitor for the treatment of genotype 1 chronic HCV infection. Although knowledge of the host genotype already facilitates clinical decisions in certain situations, common guidelines for pretreatment genotype testing still have to be defined.

back to top

RELEVANCE OF THE IL28B GENOTYPE IN THE ERA OF DIRECT-ACTING ANTIVIRALS

Zeuzem S, Soriano V, Asselah T, et al. SVR4 and SVR12 with an interferon-free regimen of BI 201335 and BI 207127, +/- ribavirin, in treatment-naïve patients with chronic genotype-1 HCV infection: interim results of SOUND-C2. Presented at: 47th Annual Meeting of the European Association for the Study of the Liver; April 18-22, 2012; Barcelona, Spain. Abstract 101.

View report

Zeuzem and colleagues presented an interim analysis of the findings from SOUND-C2—a randomized, open-label, phase IIb study evaluating the efficacy and safety of IFN-free combination therapies for patients with chronic hepatitis C .[1] In six different study arms, 362 treatment-naïve patients infected with HCV genotype 1 were treated for up to 40 weeks. Two-thirds of the participants were infected with genotype 1b, 25% had host genotype *IL28B*-CC (favorable), and approximately 10% were enrolled with compensated liver cirrhosis. The patients were stratified by HCV subtype (ie, genotype 1a or 1b), as well as by *IL28B* genotype (CC or non-CC with respect to SNP rs12979860). In the study, BI 201335, a second-wave protease inhibitor, was administered once daily along with BI 207127, a nonnucleoside NS5B polymerase inhibitor that was administered either twice or three times daily—with or without RBV. The primary endpoint of the study was SVR; the current interim analysis reported SVR through posttreatment week 4 (SVR4) for the 40-week arm and SVR through posttreatment week 12 (SVR12) for all other treatment arms.

A considerably lower SVR rate was reported with dual therapy without RBV (BI 201335 + BI 207127; SVR, 39%) compared with all arms that received triple therapy (BI 201335 + BI 207127 + RBV; SVR, 56% to 68%). Regarding dosing of BI 207127, the single twice-daily treatment arm (600 mg twice daily for 28 weeks) experienced the best overall efficacy (SVR, 68%). Among the three-times-daily treatment arms, SVR rates were similar (600 mg three times daily; 16 weeks: SVR, 59%; 28 weeks: SVR, 61%; 40 weeks: SVR, 56%; all triple therapy). Subgroup analyses revealed that SVR rates were comparably high in all HCV genotype 1b (IL28B-CC: SVR, 82% and non-CC: SVR, 84%) and genotype 1a/ IL28B-CC (SVR, 75%) patients, but much lower in those with genotype 1a/ *IL28B*-non-CC infection (SVR, 32%). Triple therapy was reportedly well tolerated, with anemia rates of 0% to 4% reported. Therapy was discontinued because of adverse events in 4.9% to 24.7% of patients (at 16 weeks and 40 weeks, respectively).

The interim analysis of the SOUND-C2 study strongly supports the high efficacy and safety of the combination of RBV and the novel DAAs BI 201335 and BI 207127 for the treatment of genotype 1 chronic HCV infection. The results emphasize the importance of RBV as a potent component of "antiviral cocktails." These findings, in conjunction with a favorable adverse effect profile, underscore the ongoing paradigm shift in hepatitis C therapy away from IFN-based treatments to DAA combination regimens that lack IFN. These therapies are expected to become a clinical reality very soon.

IL28B-associated genetic variation has previously been identified as highly predictive of response to hepatitis C therapy with Peg-IFN and RBV. The current study demonstrates a marked effect of the *IL28B* genotype on outcomes in patients with HCV genotype 1a infection, even with IFN-free therapy. Although the causative mechanism for the *IL28B* effect remains unclear, these findings suggest a pivotal role of innate immunity in the final clearance of HCV, even during therapy whose sole posited mechanism of action is inhibition of viral replication. The authors suggest that the final "act" of clearance of remnant viral reservoirs in the liver with somewhat less-than-optimal treatment regimens requires a robust innate antiviral response in order to surmount the SVR bar. It will be of great interest to determine whether this differential outcome remains a consistent finding as DAA regimens that use combinations of different classes of drugs advance into clinical practice. It would appear that until a truly "one-size-fits-all" regimen with powerful antiviral effects under all conditions is developed, pharmacogenomic tools, at least in the near future, could still have utility in helping to make the decision about whether to treat and with what regimen. We eagerly await the results of these studies.

Reference

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back to top

SNP INFLUENCES RISK FOR CHRONIC LIVER INJURY IN HEPATITIS C

Trépo E, Pradat P, Potthoff A, et al. Impact of patatin-like phospholipase-3 (rs738409 C>G) polymorphism on fibrosis progression and steatosis in chronic hepatitis C. Hepatology. 2011;54(1):60-69.

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According to a recent GWAS, a SNP in the PNPLA3 gene (patatin-like phospholipase domain-containing 3—a triglyceride lipase—affects the risk for hepatic steatosis. The same SNP was also shown to influence the severity of fibrosis in nonalcoholic fatty liver disease. In the current study, 537 Caucasian patients with chronic HCV infection who had undergone ≥ 1 pretreatment liver biopsy were recruited from 3 European centers and genotyped for the *PNPLA3* (rs738409 C > G) SNP. Infection with HCV genotype 3 was an exclusion criterion. Study endpoints were defined as fibrosis stage (F0 to F4), fibrosis progression (ratio of METAVIR score to estimated duration of disease), and steatosis.

The frequency of the minor G allele was significantly higher in patients with severe fibrosis/cirrhosis (stages F3/F4; *P* = .021). The risk for the presence of fibrosis (any stage) was not increased significantly in G allele carriers but was increased among GG homozygotes (*P* = .008). Overall, 71 % of GG patients were fibrosis progressors, compared with 50% of CG individuals and 47% of CC individuals. Unlike with the *IL28B* genotype, therapeutic response in hepatitis C was not associated with the *PNPLA3* genotype.

The pace of progression to advanced fibrosis varies widely among patients with CHC. Such clinical parameters as older age, male sex, and alcohol abuse increase a person's risk for fibrosis progression but are relatively poor indicators. A recent GWAS[1] identified a SNP (rs738409 C > G) in the *PNPLA3* gene as the strongest predictor of human steatosis. In the current study, the role played by the *PNPLA3* gene in predicting steatosis and fibrosis in patients with HCV infection has been evaluated, with results demonstrating that the G allele and homozygosity for G are associated with steatosis, the presence and severity of liver fibrosis, and progression of fibrosis. The *PNPLA3* genotype may therefore represent a predictor of liver injury in patients with chronic HCV, as well as a potential therapeutic target.

Reference

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back to top