Reply. In 1985, Drs Chu, Liaw, and colleagues described the first phase of chronic hepatitis, referred to as immune tolerant (IT), as “the high replicative phase, characterized by HBeAg reactivity in serum and only minor histologic activity,” including nonspecific reactive hepatitis and chronic persistent hepatitis. The high virus titers in IT patients ($\geq 10^9$/mL) and minimal liver damage were taken as evidence that there was no immune activity against infected hepatocytes. The IT designation was reasonable, considering evidence then available.

However, the IT designation is often equated to and treated as benign, a premise for which there is no proof. Our recent study, including experimental approaches not available in the 1980s, reexamined the concept of an IT phase, from an immunologic point of view and from direct molecular and histologic examination of liver biopsies. This report has sparked a debate on the IT phase that in our opinion is long overdue. However, Professor Liaw’s letter fails to consider our recent data in their entirety and instead focuses on historical data.

Our objection to the IT designation can be summarized as follows.

- Patients considered IT can have histologic activity and levels of fibrosis no different from those in the immune active phase. Thus, infection is not necessarily benign in the IT phase.

- We found an unexpected level of HBV-DNA integration in IT patients. Integration is widely considered an initiation event in the progression to hepatocellular carcinoma. Irrespective of the accuracy of this viewpoint, integration seems to be a surrogate marker for a much higher level of damage to host DNA.

- We observed a level of clonal hepatocyte expansion in IT patients unexplained by normal levels of hepatocyte turnover. Clonal hepatocyte expansion is a risk factor for hepatocellular carcinoma (see Marongiu et al for a review). Although chronic carriers, infected at birth or in early childhood, typically remain in the IT phase for $\geq 15$ years, even nonspecific reactive hepatitis or chronic persistent hepatitis could, over $\geq 15$ years, account for a considerable excess of clonal hepatocyte expansion.

- The number of peripheral anti-HBV T cells did not differ significantly between patients in the IT versus the immune active phase, supporting the possibility that T cells capable of destroying hepatocytes are already present in the IT phase.

Importantly, we never stated, as argued by Milich in his commentary, that young IT chronic hepatitis B patients have no defect in HBV-specific T-cell immunity. Chronic hepatitis B is characterized by defects of HBV-specific T-cell immunity and, as such, all patients present a degree of “HBV-specific immunologic tolerance.” The fact remains that measurement of peripheral HBV-specific T cells in young patients considered IT reveals an HBV-specific T-cell profile that is not clearly different than in immune active patients and may even be more conserved. We acknowledge that our data did not directly measure intrahepatic HBV-T-cell immunity, but we would respectfully point out that the data around cytoplasmic/membranous HBV core antigen expression referred to by Dr Liaw to support an IT state within the liver has no immunologic basis. The localization of HBV antigens is not an indication of HBV-specific T-cell activation because CD8 T cells recognize antigen fragments associated with HLA class I molecules and can be activated by a single HLA class I viral peptide complex. Furthermore, historical data show that HBV core-specific CD8 T cells can recognize target cells synthesizing only the secretory HBeAg, which does not accumulate in the cytoplasm or membrane of infected hepatocytes.

In summary, we understand Dr Liaw’s view of the “time-honored” IT phase, based on his historical perspective, but believe that our data justify a thorough reevaluation of this early disease phase and current treatment recommendations, given that antiviral therapy with nucleos(t)ide analogs could have long-term benefits, not just in prevention or reversal of fibrosis/cirrhosis, but also in reducing the development of hepatocellular carcinoma. In the era of personalized medicine, the blanket exclusion of IT patients as treatment candidates is an anachronism. Moreover, IT patients may benefit most from novel immune-based therapies where residual HBV immunity is less constrained by the inflammatory liver microenvironment, including immunosuppressive effects, present in the immune active phase. Modification of the IT designation would help to focus more experimental attention on the early phase of chronic hepatitis B infection. Although the IT designation has been useful for a long time, our study argues that it is no longer and may actually be harmful if it maintains the untested idea that the IT phase is also benign.

References

Conflicts of interest
The authors have made the following disclosures: Y.F. Liaw has involved in clinical trials or served as a global advisory board member of Roche. Chia-Ming Chu has no relevant conflict of interest issue.

http://dx.doi.org/10.1053/j.gastro.2016.11.057
Dear Editors:

I believe that further comments are appropriate about the need of a new classification of portal vein thrombosis (PVT) in patients with cirrhosis, as discussed in the interesting paper recently published in *Gastroenterology.*

At present, the prognostic value of PVT on cirrhosis outcomes still remains an unresolved issue. In fact, although a recent meta-analysis from the United States reporting that PVT significantly affected both mortality and hepatic decompensation, despite the weakness of enrolling studies with heterogeneous populations (partial and branch PVT were excluded or partial and total PVT were mixed), another group reported a study on an association between PVT and survival in cirrhosis, in which a systematic review of 13 selected studies was reported. However, contrary to what the authors proposed to do, a meta-analysis was not conducted because the modes of data expression and lengths of follow-up among the studies were considered heterogeneous.

Therefore, the prognostic value of PVT in cirrhosis is not a trivial point, since it influences considerations regarding the opportunity to prevent and/or treat PVT in cirrhosis and, unless future studies add further evidence, the recommendation to treat PVT in patient with cirrhosis should probably be reserved to selected cases.

In conclusion, further studies are needed to evaluate whether PVT has a prognostic value in outcomes of cirrhosis, and, at the present time, current proposals of classification of PVT in cirrhosis seem to lack clinical relevance.

ANDREA MANCUSO
Medicina Interna 1
ARNAS Civico – Di Cristina – Benfratelli
Palermo

Epatologia e Gastroenterologia, Ospedale Niguarda Ca’ Granda
Milano, Italy

References


Conflicts of interest
The author discloses no conflicts.

http://dx.doi.org/10.1053/j.gastro.2016.09.067

Reply. We are thankful to Dr Mancuso for showing interest in our recently published commentary entitled “Toward a Comprehensive New Classification of Portal Vein Thrombosis in Patients With Cirrhosis.”

Classification of Portal Vein Thrombosis in Cirrhosis

Dear Editors:

I believe that further comments are appropriate about the need of a new classification of portal vein thrombosis (PVT) in patients with cirrhosis, as discussed in the interesting paper recently published in *Gastroenterology.*

At present, the prognostic value of PVT on cirrhosis outcomes still remains an unresolved issue. In fact, although a recent meta-analysis from the United States reporting that PVT significantly affected both mortality and hepatic decompensation, despite the weakness of enrolling studies with heterogeneous populations (partial and branch PVT were excluded or partial and total PVT were mixed), many other retrospective studies have showed no impact of PVT on liver transplant waiting list mortality. Finally, a prospective multicenter study on 1243 patients with cirrhosis reported that PVT was not a prognostic factor for either mortality or hepatic decompensation. As a consequence, although PVT is generally associated with a bad prognosis for cirrhosis, it is not evident whether this reflects the fact that PVT easily arises in the context of severe liver failure or whether PVT worsens hepatic function by reducing portal flow within a context of already reduced hepatic functional reserve, thus negatively affecting survival. Moreover, the former hypothesis is highlighted by the recent concept of a prothrombotic condition being strictly linked to liver disease and recently recognized as an important issue in cirrhosis, a clinical condition traditionally considered to be affected by a bleeding diathesis. Is in important to note that the topic of whether PVT does or does not affect the natural history of cirrhosis was one of the main topics of a monothematic special issue on splanchnic vein thrombosis recently published and coordinated by an international panel committee. In that issue, parallel to the one from United States, another group reported a study on an association between PVT and survival in cirrhosis, in which a systematic review of 13 selected studies was reported. However, contrary to what the authors proposed to do, a meta-analysis was not conducted because the modes of data expression and lengths of follow-up among the studies were considered heterogeneous.

Therefore, the prognostic value of PVT in cirrhosis is not a trivial point, since it influences considerations regarding the opportunity to prevent and/or treat PVT in cirrhosis and, unless future studies add further evidence, the recommendation to treat PVT in patient with cirrhosis should probably be reserved to selected cases.

In conclusion, further studies are needed to evaluate whether PVT has a prognostic value in outcomes of cirrhosis and, at the present time, current proposals of classification of PVT in cirrhosis seem to lack clinical relevance.

ANDREA MANCUSO
Medicina Interna 1
ARNAS Civico – Di Cristina – Benfratelli
Palermo

Epatologia e Gastroenterologia, Ospedale Niguarda Ca’ Granda
Milano, Italy

References


Conflicts of interest
The authors disclose no conflicts.

http://dx.doi.org/10.1053/j.gastro.2017.03.002