Correction of insulin resistance in chronic hepatitis C patients not responding to the standard of care: More questions than answers

To the Editor:

We read with interest the comment by Serfaty and collaborators on our previous paper, and congratulate them for the successful outcome of this interesting case. We fully agree that our approach may have been inadequate and concur that, based on this case report and on other recent data [1–3], the pharmacological correction of the level of insulin resistance prior to retreatment with antivirals should be more aggressive, and possibly precede the administration of the interferon-alpha/ribavirin combination, until a HOMA score associated with a higher rate of sustained virological response has been reached [4,5].

It is noteworthy that the patient described by Serfaty and colleagues was infected by the genotype 3a of HCV. In in vitro models [6], the mechanism of virally-associated insulin resistance has been reported to be HCV genotype-specific, the genotype 3a being partly associated with the downregulation of peroxisome proliferator-activated receptor (PPAR)-γ. Treatment of transfected cells with a PPAR-γ agonist (rosiglitazone) partially reverted the suppression of the insulin signaling associated with the expression of the HCV core protein [6]. Thus, it is possible that the insulin sensitizing therapy should be tailored according to the infecting HCV genotype. In the INSPIRED-HCV trial, only one patient was infected with genotype 3a. This patient had extensive fibrosis and a mild steatosis affecting 20% of hepatocytes, but no overweight or arterial hypertension. Quite oddly, upon retreatment, her HOMA-IR score underwent a surge from 2.65 to 11, while serum HCV RNA level remained unmodified. We fear that this paradoxical increase may have been the consequence of a pharmacological interaction between interferon-alpha and two additional drugs, i.e. duloxetine and zopiclone, which have been occasionally associated with glucose metabolism derangements [6].

We remain convinced that correcting insulin resistance is a rational option in chronic hepatitis C patients failing to respond to combination therapy. However, the modalities of this correction have to be fully explored. The sequential administration of higher doses of insulin sensitizers seems a reasonable approach, but the likely genotype specificity of the mechanisms underlying the insulin resistant state and the risk of pharmacological interactions should both be taken in consideration before designing clinical trials. Finally, one should not forget that the most effective way of correcting glucose metabolism disturbances consists in lifestyle interventions [7], such as diet modifications and increased physical activity, and that there is no excuse why chronic hepatitis C patients should be spared such interventions.

References

final results of a randomized and double-blinded trial. Hepatology 2008;48:95A.


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