directly decrease the fitness of the algorithm of the serum marker. Because of this conditional relationship, serum marker performance should at best approach accuracy of liver biopsy. Therefore, it is rather surprising to support serum markers, arguing on biopsy weakness when this tool is chosen to define the formula of serum markers. Finally, Poynard et al. suggest that screening for advanced fibrosis is a public health challenge and this can only be achieved through a moratorium of liver biopsy as a first-line estimate. Anybody would agree that screening of advanced fibrosis does not rely on liver biopsy and that non-invasive tests have excellent accuracy in this setting but there is a major difference between screening for advanced fibrosis and staging fibrosis. Non-invasive tests have shown deceptively low performance in this matter with significant overlap between adjacent stages.

The risk of performing a liver biopsy should always be discussed with regards to the potential benefit for the patient and in this context any dogmatic statement, either in favour or against it, is dangerous. Today, antiviral therapy has still limited efficacy and is associated with serious adverse effects. Therefore management of patients using only a screening procedure for advanced fibrosis, such as serum markers, will clearly lead to an obvious loss of opportunities for patients to be adequately and timely treated, a risk that surpasses the adverse events of the biopsy.

Therefore, in the present situation, non-invasive serum markers are efficient screening instruments for advanced fibrosis or cirrhosis but remain a dead end when addressing the accurate evaluation of liver damage.

References


Pierre Bedossa
Department of Pathology, Beaujon Medical Center, Assistance Publique-Hôpitaux de Paris, INSERM, U 773, Paris-Diderot University, Clichy, France
Tel.: +33 1 40875460; fax: +33 1 40870077. E-mail address: pierre.bedossa@bjn.aphp.fr

Fabrice Carrat
Epidemiology of infectious diseases, UMR-S 707, UPMC & INSERM; Public Health unit, Assistance Publique Hôpitaux de Paris, Hôpital Saint-Antoine, Paris, France


Pioglitazone as adjuvant therapy in chronic hepatitis C: Sequential rather than concomitant administration with pegylated interferon and ribavirin?

To the Editor:

We read with interest the article by Overbeck et al., published in the August issue of the Journal of Hepatology [1]. This study investigating pioglitazone as adjuvant therapy in hepatitis C patients not responding to pegylated interferon and ribavirin was terminated because no effect on viral load was observed, despite a decrease of the homeostasis model assessment (HOMA) index in some patients. We believe that there were several inadequacies in the study design that may be at the origin of the negative results. First, the dosage of pioglitazone (15 mg) was rather low. Second, because of the delayed effect of pioglitazone on insulin resistance and steatosis, starting its administration concomitantly with the antiviral therapy may be untimely [2].

Here, we report the effect of a sequential administration of pioglitazone at higher dosage upon retreatment of a patient with chronic hepatitis C and steatosis who had not responded to a prior regimen of pegylated interferon and ribavirin. A 43-year-old man with chronic HCV infection was admitted to our Department at Saint-Antoine Hospital in November 2004 for liver biopsy. Known risk factor was IV drug use between 1982 and 1990. The patient had no previous history of diabetes, dyplipidemia or hypertension. Alcohol consumption was discontinued 6 months earlier. Chronic HCV infection was diagnosed in April 2004 based on positive anti-HCV antibodies (ELISA) and detectable HCV RNA by RT-PCR (Amplicor HCV, Roche). At this time, ALT, AST
and GGT activities were 3.5 × N, 1.4 × N and 2.5 × N, respectively. At admittance, physical examination showed normal blood pressure and no overweight, the body mass index being 23.5 kg/m². Biochemistry revealed ALT activity 2.5 × N, AST 1.2 × N and GGT 2.5 × N. Prothrombin time, bilirubinemia, albuminemia and hemogram were in normal range. Fasting serum glucose, triglyceride, total and HDL cholesterol levels were in the normal range. Virological assays showed genotype 3 infection and serum HCV RNA at 215,123 IU/ml (Bayer VERSANT HCV RNA 3.0, lower limit of detection 615 IU/ml). Other causes of chronic liver disease were excluded with appropriate tests (HBV or HIV infections, genetic hemochromatosis, Wilson disease and autoimmune liver diseases). Liver US showed bright liver. Liver biopsy of adequate (25 mm) size showed chronic hepatitis with METAVIR score A2F3 and macrovacuolar steatosis involving 30% of hepatocytes. There was no evident sign of steatohepatitis and Perls’ staining was negative. Given the genotype 3 infection and a very likely virally-induced steatosis, which is not a risk factor of resistance to antiviral therapy [3], a combined regimen with pegylated interferon-α2a (180 µg QW) and ribavirin (800 mg QD) was initiated in December 2004. At week 4 of treatment, liver tests were in normal range and HCV viral load had decreased to 50,605 IU/ml but at week 12, HCV viral load had relapsed to 150,567 IU/ml. Because of partial response and good tolerance to treatment, ribavirin dosage was increased to 1 g/d for the following 12 weeks. At week 24, viral load was still positive at 44,290 IU/ml and treatment was stopped. Three months after stopping treatment, ALT and AST levels were 1.4 × N and normal, respectively, and viral load was 84,355 IU/ml. Since metabolic steatosis is associated with non-response to antiviral therapy, insulin resistance was assessed according to HOMA index, which resulted to be 4.8 (4.07 mml/l × 27 mU/22.5). We concluded that the steatosis detected in this patient was metabolic rather than virally-induced, in spite of the infection with HCV genotype 3. After obtaining informed consent, treatment with pioglitazone (Actos®, Takeda Pharmaceuticals) was initiated in November 2005 at the dosage of 45 mg per day. During treatment, there was no side effect, especially no significant weight gain. Transaminases and GGT levels progressively normalized. Lipid parameters were not significantly modified. HOMA index decreased from 4.8 to 3 and 1.3 after 3 and 5 months, respectively. Then, after 5 months of pioglitazone pre-treatment, a combination therapy with pegylated interferon-α2a (180 µg QW) and ribavirin (1000 mg QD) was added for a total duration of 48 weeks. At this time, viral load was assessed by real time PCR (Taqman Roche, lower limit of detection 15 IU/ml). Starting with a level of 1,113,119 IU/ml prior to initiating the second course of combination therapy, the viral load decreased to 68,558 IU/ml after 4 weeks of triple therapy. After 12 weeks, HCV RNA was undetectable and remained negative until the end of treatment. Pioglitazone and combined antiviral therapy were well tolerated without necessitating dose reductions or discontinuation. Treatment was stopped in March 2007. Six months after the end of treatment, transaminases were in normal range, HCV RNA was still undetectable and HOMA index remained lower than 2 (Fig. 1).

In this case report, improvement of insulin sensitivity with pioglitazone was associated with sustained virological response in a patient previously not responding to pegylated interferon and ribavirin, confirming the possible role of insulin resistance in the sensitivity to interferon [4]. Prior to initiating the second course of antiviral therapy, a several month-course of pioglitazone 45 mg/d was required in order to significantly reduce insulin resistance levels, as assessed by the HOMA index, as previously shown in patients with NASH [2]. In order to minimize potential bias, the same pegylated interferon and the same dosages were used during the first and the second course of combination therapy with similar adherence to treatment. Since we cannot exclude that virological response during the second course of combination therapy may be simply the result of retreatment, randomized placebo controlled trials are warranted before definitive conclusions can be drawn. A multicenter trial assessing the effect of sequential administration of pioglitazone on the response to antiviral therapy in naïve HCV patients with insulin resistance is currently being conducted in France.
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