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Case report

Pioglitazone in chronic hepatitis C not responding to pegylated interferon-α and ribavirin☆

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***Background/Aims*: Insulin resistance reduces the response to interferon alfa-based therapy of chronic hepatitis C patients. It has been speculated that improvement of insulin sensitivity might increase the chances of responding to treatment of such individuals.**

***Methods*: We started a multicenter clinical trial of retreatment of chronic hepatitis C patients, who had failed to respond to the pegylated interferon alfa/ribavirin combination, with a triple therapy consisting in these same antivirals plus an insulin-sensitizer (pioglitazone) (The INSPIRED-HCV study).**

***Results*: None of the first five patients fulfilling the inclusion criteria and included in the trial had a satisfactory virological response after 12 weeks of retreatment, despite the fact that in at least three of them the insulin resistance score improved. As a result, the study was terminated.**

***Conclusions*: Different schedules are warranted to improve insulin sensitivity prior to attempting retreatment of chronic hepatitis C patients with insulin resistance.**

***Keywords*: Hepatitis C non-responders; Retreatment; Insulin resistance; Pioglitazone; Chronic hepatitis**

1. Introduction

Insulin resistance and diabetes are major disease modifiers in chronic hepatitis C, as they increase liver fibrogenesis [1–4] and reduce the rate of response to antivirals [5–7]. Regarding the latter, a sustained virological response (SVR) was reported to occur in 23 of 70 (32.8%) of patients with genotype 1 and insulin resistance (measured as homeostasis assessment of insulin resistance, HOMA-IR > 2) vs. 26 of 43 (60.5%) of genotype 1 patients without insulin resistance ($p = .007$; OR, 3.12, 95% CI, 1.42–6.89) [5]. These findings were independently confirmed [6] and recently extended to non-responders with genotypes 2 and 3 [7]. Thus, based on our recent results [7], we [7,8] and others [5] have suggested that insulin resistance should be corrected in patients with chronic hepatitis C not responding to currently available antiviral treatment, in order to improve response to retreatment. The modalities of this intervention, however, have not been established. In addition, the optimal HOMA-IR score to be attained has not been identified.

We planned a prospective, multicenter study to investigate the efficacy and safety of the insulin-sensitizer

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pioglitazone (Actos™, Takeda Pharma AG, Lachen, Switzerland) 15 mg QD, added to the pegylated interferon-α_{2a} (PEG-IFN-α_{2a}) (Pegasys™, Roche Pharma Schweiz AG, Reinach, Switzerland) 180 μg QW/ribavirin (Copegus™, Roche) 1000–1200 mg QD combination therapy in chronic hepatitis C patients who had previously failed to respond (i.e. had detectable serum HCV RNA after 12 weeks of therapy) to a pegylated interferon-α/ribavirin combination without the insulin-sensitizer (“A pilot study of treatment with pegylated interferon-alpha$_{2a}$, ribavirin and insulin-sensitizer pioglitazone of insulin resistance (with the exception of diabetes) in hepatitis C virus infection”, The INSPIRED-HCV study, registered as NCT00433069 at Clinicaltrials.gov). All patients had a baseline HOMA-IR score >2 as additional inclusion criterion, because this was the threshold discriminating responders from non-responders in previous works [5,7]. Diabetic patients were excluded. The trial was approved by the Ethical Committee of the University Hospitals of Geneva, and all patients consented to participate.

2. Multiple case reports

Patient #1 was a 46-year-old female who had failed previous treatment of Pegasys™ and Copegus™ four years earlier. A liver biopsy performed in 2004 showed a Metavir score of A2 F3, with mild steatosis affecting 20% of hepatocytes. She had a normal body weight with a BMI of 20.8, and was not known for a hypertension or a dyslipidemia. As concomitant medications, she was receiving duloxetine 60 mg QD and zopiclone 7.5 mg QD. After 12 weeks of treatment, serum HCV RNA level did not change (from 176,000 IU/ml to 154,000 IU/ml, measured by Cobas TaqMan HCV, Roche Diagnostics, Rotkreuz, Switzerland) and, oddly enough, the HOMA-IR score increased from 2.65 to 11. Thus, therapy was discontinued. Her body weight remained stable during therapy.

Patient #2 was a 49-year-old male with a liver biopsy performed in 2003 that showed a mild chronic hepatitis, focal interface hepatitis, mild steatosis and a Metavir fibrosis score of F3. Prior to this biopsy, in 2001, he had been enrolled in an international clinical trial [9] where he had received Pegasys™ and Copegus™ at the same doses tested in the INSPIRED-HCV study. Immediately before enrolment in the latter, the liver stiffness (measured by FibroScan, Echosens, Paris, France) was 11.1 kPa. At baseline, the patient had a serum HCV RNA level of 11,000,000 IU/ml (genotype 1b), a HOMA-IR score of 4.64, a marked overweight (98 kg, 182 cm for a BMI of 29.6 and a waist circumference of 120 cm), but no dyslipidemia (serum total cholesterol 5.4 mmol/L, triglycerides 0.3 mmol/l and HDL cholesterol 2.0 mmol/l) nor arterial hypertension (145/85 mm Hg). After 12 weeks of therapy, the HCV RNA and the HOMA-IR decreased, respectively, to 64,000 IU/ml and 2.66. The body weight fell to 88 kg and the waist circumference to 111 cm. No dose changes of the three drugs had been necessary, as they were all sufficiently well tolerated. Despite the fall in viral load, the patient had his therapy discontinued. In fact, the −2.23 Log reduction in serum HCV RNA was superimposable to that observed on occasion of the first treatment six years before (−2.24 Log), when no pioglitazone had been added.

Patient #3 was a 59-year-old female, with histologically documented cirrhosis and a mild steatosis, functionally compensated, related to a HCV genotype 1b infection. She had no overweight (62 kg, waist circumference 83 cm), no arterial hypertension and a baseline HOMA-IR score of 5.71. Treatment was very well tolerated, with no dose reductions. After 12 weeks of therapy, the HOMA-IR score decreased slightly to 4.52, while serum HCV RNA went from 410,000 to 61,000 IU/ml. All treatment were stopped. Body weight and waist circumference were virtually unchanged (63 kg and 82 cm at week 12).

Patient #4 was a 50-year-old male with histologically proven cirrhosis, mildly overweight (BMI 25.6, waist circumference 93 cm) and a poorly controlled arterial hypertension discovered one year prior to enrolment. At this time, he was taking lisinopril 20 mg QD and hydrochlorothiazide 12.5 mg QD but blood pressure was 170/115 mmHg. Serum cholesterol and triglycerides were within the normal ranges, but HDL cholesterol was low (0.5 mmol/L). The baseline HOMA-IR score was 3.79 and serum HCV RNA 1,100,000 IU/ml (genotype 1b). Antiviral treatment was rather well tolerated, with mild fatigue not necessitating drug dose modifications. After 12 weeks, the HOMA-IR was virtually unchanged (3.57) but HCV RNA had fallen to 11,000 IU/ml. Since during a previous course of antiviral treatment the viremia had decreased by less than 1 Log, we resorted to continue the triple therapy. After 24 weeks, however, viremia had increased slightly to 42,000 IU/ml and all treatment were definitely stopped. Body weight remained unchanged throughout the whole course of therapy.

Patient #5 was a 46-year-old male. A liver biopsy carried out one year before enrolment had shown mild activity and portal fibrosis (Metavir A1 F1), with a mild steatosis affecting 20% of hepatocytes. The patient had received a 12-week course of combination with Pegasys™ and Copegus™ resulting in a −0.95 Log change in his serum HCV RNA level one year prior to enrolment. His baseline HCV RNA was 2,700,000 IU/ml (genotype 1a), and the HOMA score 2.88. He had normal body weight (60 kg, waist circumference 87 cm) and normal blood pressure. As concomitant medications, he was receiving olanzapine 15 mg QD and escitalopram