Towards optimal treatment for chronic hepatitis C infection
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High incidence of type 1 diabetes mellitus during or shortly after treatment with pegylated interferon alfa for chronic hepatitis C virus infection

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Online Early, Liver International DOI:10.1111/j.1478-3231.2007.01610.x
High incidence of type 1 diabetes mellitus during or shortly after treatment with pegylated interferon \( \alpha \) for chronic hepatitis C virus infection

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Keywords
autoimmune – diabetes mellitus – hepatitis C – interferon \( \alpha \)

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Received 29 April 2007
accepted 9 September 2007

DOI:10.1111/j.1478-3231.2007.01610.x

Abstract

Background: Development of diabetes mellitus (DM) during or shortly after treatment with interferon \( \alpha \) (IFN-\( \alpha \)) in patients with chronic hepatitis C virus (HCV) infection has been reported sporadically. We prospectively screened for DM during and after IFN-\( \alpha \) therapy for chronic HCV infection. Methods: Blood glucose levels of patients with chronic HCV infection were routinely assessed at all outpatient visits during and after treatment with pegylated-IFN-\( \alpha \) (Peg-IFN-\( \alpha \)) and ribavirin (Riba). Results: Between December 2002 and October 2005, 189 non-diabetic patients were treated with Peg-IFN-\( \alpha \)/Riba, of whom five developed type 1 DM (2.6%), three type 2 DM (1.6%) and one an indeterminate type of DM. Classical symptoms of DM were present in three patients who developed DM shortly after cessation of Peg-IFN-\( \alpha \)/Riba. In the other patients, symptoms of DM were either indistinguishable from side effects caused by Peg-IFN-\( \alpha \)/Riba or absent. Conclusion: Our study showed a high incidence of type 1 DM during Peg-IFN-\( \alpha \)/Riba therapy for chronic HCV infection. Symptoms of DM may be absent or mistaken for Peg-IFN-\( \alpha \)/Riba-associated side effects. To diagnose DM without delay, we propose routine assessment of blood glucose at all outpatient visits during and after Peg-IFN-\( \alpha \)/Riba treatment in chronic HCV patients.

Interferon \( \alpha \) (IFN-\( \alpha \)) and ribavirin (Riba)-based therapy for chronic hepatitis C virus (HCV) infection is effective in 40–80% of patients but causes a wide range of side effects, such as influenza-like symptoms, depression, insomnia, headache, fatigue, fever and anaemia (1). IFN-\( \alpha \) treatment for chronic HCV infection is associated with the development of autoimmune disorders such as autoimmune thyroiditis, hypothyroidism, hyperthyroidism and Sjögren’s syndrome in 2.5–20% of patients (1, 2). Type 1 diabetes mellitus (DM) can also occur during or after IFN-\( \alpha \) treatment for chronic HCV infection. Several cases have been published (3–10), but the exact incidence of DM during or after treatment with IFN-\( \alpha \) is unknown. An Italian retrospective study among 11,241 patients with chronic HCV infection treated with IFN-\( \alpha \) revealed only 10 new diagnoses of DM (0.08%) after at least 16 weeks of treatment (11). Development of type 1 DM during treatment with IFN-\( \alpha \) for chronic hepatitis B infection, hairy cell leukaemia, Kaposis’s sarcoma and renal cell carcinoma has also been reported (3), but the majority of cases occurred in patients with chronic HCV infection (3).

The prevalence of type 2 DM was found to be significantly higher in a cohort of IFN-\( \alpha \)-naïve chronic HCV patients (14.5%) compared with patients suffering from other chronic liver diseases (7.3%) and the general population (7.8%); the difference was even more pronounced in patients with advanced histological disease (12, 13). Recent studies have shown that insulin resistance is common in non-diabetic chronic HCV patients, and that insulin resistance decreases during treatment with IFN-\( \alpha \) (14–18).

We screened for DM during and after treatment with pegylated-IFN-\( \alpha \) (Peg-IFN-\( \alpha \)) and Riba for

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Liver International (2007)
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chronic HCV infection. This started after we observed two index cases of DM during Peg-IFN-α/Riba treatment in our hospital in December 2002. In the first patient, DM-related symptoms, commencing after 16 weeks of antiviral treatment, had been attributed to Peg-IFN-α/Riba; DM was diagnosed because symptoms were persistent after cessation of Peg-IFN-α/Riba treatment. The second patient was presented at the emergency room after 11 weeks of Peg-IFN-α/Riba therapy because of severe debilitation, where DM was diagnosed (blood glucose 54 mmol/L). Because of the atypical clinical picture of DM in these two patients, we amended our treatment protocols, and blood glucose levels of patients with HCV were routinely measured in all patients at all outpatient visits before, during and after treatment with Peg-IFN-α/Riba as of December 2002.

Methods

Treatment protocols

Patients were treated with either (i) standard therapy consisting of Peg-IFN-α2b 1.5 μg/kg/week (PegIntron®, Schering-Plough Corporation, Kenilworth, NJ, USA) or Peg-IFN-α2a 180 μg/week (Pegasys®, Roche, Basel, Switzerland) combined with Riba (Rebetol®, Schering-Plough or Copegus®; Roche) 1000–1200 mg daily for a total of 24 or 48 weeks according to HCV genotype (n = 107) or (ii) in a clinical trial with triple therapy consisting of amantadine hydrochloride (Symmetrel®, Novartis Pharma, Arnhem, the Netherlands) 200 mg daily and Riba 1000–1200 mg daily for a total of 24 or 48 weeks, combined with high-dose IFN-α induction (IntronA®, Schering-Plough) during the first 6 weeks (week 1–2: 18 MU daily, week 3–4: 9 MU daily, week 5–6: 6 MU daily), thereafter combined with Peg-IFN-α2b 1.5 μg/kg/wk for a total of 24 or 48 weeks (n = 100). In the group receiving standard therapy (n = 107), 17 patients had been treated with IFN-α previously, 90 were treatment naïve, 34 were female and 73 male; 95 were treated with PegIntron and Rebetol, 1 with IntronA and Rebetol, and 11 with Pegasys and Copegus. In the group receiving triple therapy (n = 100), 46 patients had been treated with IFN-α previously, 54 were treatment naive, 23 were female and 77 male.

Assessment of blood glucose levels

Random blood glucose levels of patients with HCV were routinely measured at all outpatient visits before, during and after treatment with Peg-IFN-α/Riba as of December 2002.

Determination of autoantibodies

In patients who developed DM, we retrospectively determined autoantibodies to glutamic acid decarboxylase (anti-GAD65), protein tyrosine phosphatase (anti-IA2) and pancreatic islet cells [islet cell antibodies (ICA)] in stored plasma samples obtained before and after development of DM. Detection of anti-GAD65 and anti-IA2 was performed by a fluid phase assay using [35]S-labelled recombinant human GAD65 and IA2 as tracers, and protein A sepharose beads for precipitation. Anti-GAD65 and anti-IA2 values were determined according to the WHO 97/550 standard (19). ICA was determined by indirect immunofluorescence on monkey pancreas tissue (INOVA Diagnostics, San Diego, CA, USA). Anti-GAD65 and anti-IA2 test results were noted in international units (IU) per millilitre and converted to negative, indeterminate, weakly positive or positive. The following cut-off values (in IU/mL) were used: for anti-GAD65, 0–29 = negative, 30–42 = indeterminate, 43–80 = weakly positive and > 80 = positive; for anti-IA2, 0–23 = negative, 24–46 = indeterminate, 47–68 = weakly positive and > 68 = positive. Seroconversion was defined as a transition from a negative or an indeterminate state to a (weakly) positive state.

Autoantibodies directed to thyroid peroxidase (anti-TPO) and antinuclear antibodies (ANF) were measured using standard immunoassays before antiviral therapy. In patients who developed DM with seroconversion, anti-TPO was measured again. Thyroid function (throid-stimulating hormone and free T4) was tested before treatment and every 3 months during treatment in all patients according to standard recommendations.

Human leucocyte antigen typing

In those who developed DM, the human leucocyte antigen (HLA) haplotype was analysed using PCR with sequence-specific primers (SSP, GenoVision, West Chester, PA, USA) and sequence-specific probes (SSO, Dynal, Carlsbad, CA, USA) on stored or fresh peripheral blood mononuclear cells.

C-peptide reserve

In those who developed DM, C-peptide levels were measured before and after glucagon stimulation to assess the degree of pancreatic islet cell destruction (20). Briefly, an intravenous cannula was placed in the forearm of the patient in a fasting state; blood samples for assessment of C-peptide and glucose levels were
obtained 15 and 0 min before administration of 1 mg glucagon intravenously (i.v.) and 6 min afterwards.

Results
Patients
Between December 2002 and October 2005, 207 patients with chronic HCV infection were treated. One hundred and seven patients received standard antiviral therapy and 100 received triple therapy. Eighteen patients already suffered from DM before therapy and were therefore excluded from this analysis. One hundred and eighty-nine patients were analysed, including the two index patients and including 24 patients who were either already on treatment or during the 24-week follow-up period to determine the virological response, when the study started in December 2002.

In total, nine of 189 patients (4.8%) developed DM defined as two random glucose samples above 11.1 mmol/L, according to the ADA classification (21). All 189 patients had normal glucose levels at baseline. Type 1 DM was defined as the presence of associated autoantibodies with or without susceptible HLA constitution; type 2 DM was defined as the absence of associated autoantibodies and no susceptible HLA constitution. Five patients (2.6%) developed type 1 DM, and three patients (1.6%) developed type 2 DM. One patient without autoantibodies but with a susceptible HLA-constitution DM could not be labelled as type 1 or 2; this patient declined assessment of C-peptide reserve. Five of 98 patients (5.1%) developed DM during \((n = 4)\) or after \((n = 1)\) standard treatment, and four of 91 patients (4.4%) during \((n = 2)\) or after \((n = 2)\) triple treatment.

Patient characteristics are summarized in Table 1. Classical symptoms of DM were indistinguishable from the side effects of antiviral therapy with Peg-IFN-\(\alpha\)/Riba in these patients. Three patients presented with typical symptoms (e.g. thirst and polyuria), but they developed DM 4 weeks after cessation of treatment, when Peg-IFN-\(\alpha\)/Riba-related side effects had disappeared.

All nine patients were initially treated with insulin. After cessation of antiviral therapy, seven patients remained insulin dependent, whereas two patients without detectable antibodies (Table 2, patients 1 and 2) switched to oral antidiabetic drugs. One of these two patients was even able to stop oral antidiabetic drugs after losing weight. Peg-IFN-\(\alpha\)/Riba treatment was stopped prematurely when DM was diagnosed in two of nine patients. Three patients achieved a sustained virological response, defined as undetectable HCV RNA 24 weeks after cessation of antiviral therapy.

β-cell autoantibodies
As depicted in Table 2, two of the nine patients were positive for anti-GAD65 or ICA before treatment. Three of the nine patients seroconverted for anti-GAD65, anti-IA2 or ICA during treatment.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>BMI (kg/m²)</th>
<th>DM in family</th>
<th>HCV genotype</th>
<th>Previous IFN-(\alpha)</th>
<th>Cirrhosis</th>
<th>Antiviral treatment</th>
<th>Onset of DM</th>
<th>Virologic outcome</th>
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<td>Week 11</td>
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</tr>
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<td>33</td>
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<td>–</td>
<td>+</td>
<td>Standard</td>
<td>4 weeks after ET</td>
<td>NR</td>
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<td>Week 22</td>
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<td>+</td>
<td>Triple</td>
<td>4 weeks after ET</td>
<td>NR</td>
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</table>

*DM was diagnosed after cessation of Peg-IFN-\(\alpha\)/Riba, but based on symptoms, the onset of DM was estimated after 16 weeks of antiviral treatment.
†Therapy was stopped after the development of DM.

Patients were treated for 24–48 weeks with either (i) standard therapy consisting of Peg-IFN-\(\alpha\)/Riba or (ii) in a clinical trial with triple therapy consisting of amantadine hydrochloride and Peg-IFN-\(\alpha\)/Riba, with high-dose IFN-\(\alpha\) induction instead of Peg-IFN-\(\alpha\) during the first 6 weeks.

BMI, body mass index, calculated as weight in kilograms divided by square height in metres.

DM in family, first degree family members with type 1 or 2 DM.

ET, end of treatment (24-48 weeks).

NR, non-response, defined as persistence of HCV RNA during and after antiviral treatment.

SVR, sustained virologic response, defined as undetectable HCV RNA 24 weeks after cessation of antiviral treatment.

DM, diabetes mellitus; HCV, hepatitis C virus; Peg-IFN-\(\alpha\), pegylated-interferon-\(\alpha\); Riba, ribavirin.
Incidence of DM during IFN treatment for HCV

Table 2. Type 1 diabetes mellitus-associated autoantibodies before antiviral therapy and after development of diabetes mellitus, human leucocyte antigen haplotype, C-peptide reserve, diabetes mellitus classification and non-β-cell autoantibodies in all patients who developed diabetes mellitus

<table>
<thead>
<tr>
<th>Patient</th>
<th>anti-GAD65</th>
<th>anti-IA2</th>
<th>ICA</th>
<th>Positive for anti-GAD65, anti-IA2 or ICA before treatment</th>
<th>Seroconversion for anti-GAD65, anti-IA2 or ICA during treatment</th>
<th>Risk HLA*</th>
<th>C-peptide reserve†</th>
<th>DM type</th>
<th>Anti-TPO</th>
<th>ANF</th>
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<td>No</td>
<td>ND</td>
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</tbody>
</table>

*HLA haplotype was analysed using stored or fresh PBMCs. Two patients (8 and 9) declined extra sampling of blood for these tests.
†C-peptide reserve was assessed in three patients, four patients refused the test, two patients who had developed hepatocellular carcinoma were not contacted.

Autoantibodies to thyroid peroxidase (anti-TPO) and antinuclear antibodies (ANF) were measured in stored plasma samples using standard immunoassays before antiviral therapy.

Cut-off values for autoantibodies:
- Anti-GAD65 (IU/mL)
  - 0–29 negative
  - 29–42 indeterminate
  - 42–80 weakly positive
  - > 80 positive

- Anti-IA2 (IU/mL)
  - 0–23 negative 24–46 indeterminate
  - 47–68 weakly positive
  - > 68 positive.

+ +, positive; +, weakly positive; ±, indeterminate; —, negative; seroconversion was defined as transition to a + or + + state; DM, diabetes mellitus; ANF, antinuclear antibodies.

Non-β-cell antibodies

One patient (patient 7, Table 2) developed thyroiditis, followed by hypothyroidism, without the presence of anti-TPO, shortly after the development of type 1 DM; this patient was positive for ANF before treatment. The other two seroconverters remained anti-TPO negative (data not shown).

Human leucocyte antigen typing

The human leucocyte antigen haplotype was determined in seven of the nine patients. Four patients had an HLA haplotype associated with an increased susceptibility (DR3, DR4, DQ8 and DQ2) for the development of type 1 DM. Two of these four patients with a DM-associated HLA haplotype also seroconverted for anti-GAD65 (Table 2). Two patients declined additional blood sampling for assessment of HLA haplotype.

C-peptide reserve

In three patients, we assessed the C-peptide reserve, four patients refused the test and two patients, who had developed hepatocellular carcinoma, were not contacted (Table 2). Two patients with positive β-cell autoantibodies had low fasting C-peptide levels (< 100 pmol/L) that did not increase after stimulation with 1 mg of glucagon i.v., suggesting complete destruction of pancreatic β-cells (Table 2). One patient without β-cell autoantibodies had a fasting C-peptide level of 1060 pmol/L that increased to 1700 pmol/L 6 min after stimulation with 1 mg of glucagon i.v., indicating adequate function of pancreatic β-cells (Table 2).
Chapter 6

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Ethnic origin of the type 1 diabetes mellitus patients

Two of the five patients who developed type 1 DM were of Dutch origin, one patient was born in Portugal, one patient was born in Egypt and one patient was born in Surinam.

Sex

One of 50 females (2%) vs eight of 119 (6.7%) males developed DM ($P = 0.45$, Fisher’s exact test).

Discussion

In this prospective cohort study, we found the incidence of DM, especially type 1, during or shortly after treatment with Peg-IFN-α/Riba for chronic HCV infection to be higher than reported previously. Most patients who developed DM were identified through routine assessment of blood glucose levels, as DM-related complaints were absent or mistaken for Peg-IFN-α/Riba-related side effects.

So far, 31 cases of de novo type 1 DM during or after treatment of chronic HCV infection with IFN-α, IFN-α/Riba or Peg-IFN-α/Riba have been described (3, 5–10). Through screening, we identified five certain cases and one possible case of de novo type 1 DM during or after treatment of chronic HCV infection with Peg-IFN-α/Riba.

In our study, only two of the nine patients who developed DM tested positive for type 1 DM-associated autoantibodies before IFN-α was started. These findings agree with those of Fabris et al. (3), who analysed the presence of β-cell autoantibodies in a number of studies: anti-GAD65, ICA or anti-IA2 was present in 3% of patients with chronic HCV infection (12 of 440) before treatment; two of 440 patients (0.45%) developed type 1 DM during antiviral therapy, and both tested positive for ICA before treatment (i.e. two of the 12 patients with anti-GAD65, ICA or anti-IA2 before treatment). In contrast, pretreatment autoantibodies associated with the development of type 1 DM – assessed in 26 of the 31 reported cases so far – were positive in 50% of patients who developed type 1 DM (3, 5, 9). Taken together, both the positive and the negative predictive value of β-cell autoantibodies seem too low to identify patients at a high risk or to effectively rule out the possibility of developing IFN-α-associated type 1 DM.

The destruction of pancreatic β-cells in type 1 DM may be mediated by IFN-α (22, 23). Enhanced

Fig. 1. Glucose levels and autoantibodies to glutamic acid decarboxylase (anti-GAD65) in patient 4 who developed type 1 diabetes mellitus during antiviral therapy. Glucose (mmol/L, red line) and anti-GAD65 (E/mL, grey columns). Glucose levels were assessed prospectively, autoantibodies were assessed retrospectively in stored plasma samples. Anti-GAD65 was weakly positive at baseline (46 E/mL), increased to positive (84 E/mL) before hyperglycaemia occurred at 11 weeks of treatment, and continued to increase thereafter (112 E/mL week 11, 335 E/mL week 28). Treatment with insulin was initiated immediately after the peak in blood glucose level at week 11. The broken horizontal line depicts the upper limit of normal (ULN) for non-fasting blood glucose levels (11.1 mmol/L).
expression of IFN-α by pancreatic islet cells in transgenic mice induces inflammation (22, 24), autoreactive T cells (22, 25) and precedes DM (22, 24, 26). Enhanced expression of IFN-α by pancreatic islet cells has also been demonstrated in patients with type 1 DM (27, 28). Riba and amantadine are not associated with the development of DM.

Certain HLA haplotypes (DR3, DQ2, DR4 and DQ8) are associated with increased susceptibility to type 1 DM (29). In the analysis by Fabris et al. (3), HLA haplotype was determined in 13 patients with chronic HCV infection who developed type 1 DM during IFN-α or IFN-α/Riba therapy; all 13 patients had an HLA haplotype associated with increased susceptibility to type 1 DM. In our study, four of the nine patients had a type 1 DM-associated HLA haplotype, of whom three patients also tested positive for one or more autoantibodies (Table 2). We classified one patient as indeterminate owing to the absence of autoantibodies. Taken together, these results suggest that certain HLA haplotypes may predispose to the development of type 1 DM during Peg-IFN-α/Riba therapy in chronic HCV patients. In the patients who seroconverted, the absence of concomitant anti-TPO antibodies argues against induction of a polyglandular autoimmune syndrome by IFN-α.

In addition, we described three cases of de novo type 2 DM during treatment of chronic HCV infection with Peg-IFN-α/Riba. The prevalence of type 2 DM is high among chronic HCV patients, especially in patients with advanced fibrosis or cirrhosis (12, 30). The pathogenesis is unclear, but insulin resistance and the development of DM may be mediated by pro-inflammatory cytokines such as IL-6 and TNF-α (31, 32).

Four of the nine patients who developed DM were treated with triple antiviral therapy with high doses of IFN-α during the first 6 weeks (Table 1, patients 2, 4, 5, 6); one of these patients had been treated with IFN-α previously. The incidence of DM was similar in the standard treatment group (five of 98 patients, 5.1%) compared with the triple treatment group (four of 91 patients, 4.4%). The prevalence of DM before treatment with triple therapy was higher in previous IFN-α non-responders (six of 46 patients) than in treatment-naïve patients (three of 54) but this was not significant (P = 0.29, Fisher’s exact test). The prevalence of DM before treatment with standard therapy was similar in previous IFN-α non-responders (two of 17 patients) compared with treatment-naïve patients (seven of 90, P = 0.63, Fisher’s exact test). Taken together, these findings suggest that the development of DM is not associated with higher doses of IFN-α or multiple courses of treatment.

Whether pegylation of IFN-α has an effect is uncertain. Three of the 31 previously described patients and all five patients in our study who developed type 1 DM during IFN-α treatment were treated with Peg-IFN-α (5, 6).

Our study has several limitations: (i) we only assessed type 1 DM-associated autoantibodies in patients who developed DM and (ii) we did not use a control group such as chronic hepatitis B patients undergoing IFN-α treatment, or untreated chronic HCV patients. However, our study, prompted by two index patients who developed DM during treatment for chronic HCV infection, was based on a clinical – ad hoc – adjustment of two treatment protocols to monitor development of DM. Interestingly, the two index cases in our study (patients 1 and 2), who both required insulin at the time of diagnosis, had developed type 2 DM. Five of the seven patients who were subsequently identified had developed type 1 DM. Given the low positive and negative predictive values of type 1 DM-associated autoantibodies (~50%) (3), and the similar clinical presentation of both types of DM, we chose to monitor glucose levels rather than rely on autoantibodies.

No recommendations have been made in HCV treatment guidelines on glucose assessment during therapy (33). Considering (i) the high incidence of types 1 and 2 DM in our study, (ii) the atypical clinical picture of DM during Peg-IFN-α/Riba therapy, (iii) the availability of an easy method to identify patients who develop DM and (iv) the importance of the treatment of diabetes, we suggest that routine glucose assessment at all outpatient visits for all HCV patients before, during and shortly after Peg-IFN-α/Riba treatment should be incorporated into the treatment guidelines, similar to the existing recommendation to screen for autoimmune thyroid disease.

In conclusion, this is the first prospective study on the development of DM in chronic HCV patients during treatment with Peg-IFN-α/Riba. We have shown that the incidence of DM, especially type 1, during treatment with Peg-IFN-α/Riba for chronic HCV infection is markedly higher than reported previously. DM-related complaints are frequently absent or mistaken for Peg-IFN-α/Riba-related side effects. Routine assessment of random blood glucose is an easy method to identify patients who develop DM during Peg-IFN-α/Riba treatment. These results support routine assessment of blood glucose levels at all outpatient visits before, during and in the first month after Peg-IFN-α/Riba treatment to detect DM without delay.
Chapter 6

Acknowledgements

We are grateful to Marcel Beld (Section of Clinical Virology, Department of Medical Microbiology, Academic Medical Centre, Amsterdam, the Netherlands) for providing access to stored plasma samples.

Preliminary results of these studies were presented at the 41st annual meeting of the European Association for the Study of the Liver, Vienna, Austria, 26–30 April 2006 and at the 42nd annual meeting of the European Association for the Study of Diabetes, Copenhagen/Malmö, 14–17 September 2006.

Conflict of interest statement: Dr H. W. Reesink is a consultant for Schering-Plough and has received grants from Hoffmann-La Roche and Schering-Plough. The other authors declare that they have no conflict of interest.

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