Effect of metformin and rosiglitazone on lipid metabolism in HIV infected patients receiving protease inhibitor containing HAART

J. Tomažič, P. Karner, L. Vidmar, M. Matičič, P.M. Sharma and A. Janež

Aims. Insulin resistance may be the primary event in the protease inhibitor-associated metabolic syndrome. Treatment with insulin sensitizers (metformin, rosiglitazone) can ameliorate insulin resistance. So far, the effects of these agents on blood lipids have not been well determined. The aim of the present study was to evaluate the effects of metformin and rosiglitazone treatment on lipid metabolism in HIV infected patients receiving protease inhibitors containing HAART.

Design and Methods. HIV infected male patients (>18 years) were eligible for the study if they had impaired glucose tolerance with insulin resistance, characterized by fasting insulin concentration greater than 20 mIU/L and if they were on stable antiretroviral therapy regimen including a protease inhibitor for at least 12 months prior to the study enrolment. The patients were randomly assigned to receive either 1g/day metformin (metformin group, n=30) or 4 mg/day rosiglitazone maleate (rosiglitazone group, n=30) or no treatment (control group, n=30). The primary efficacy parameters were fasting plasma lipids, glucose levels and fasting insulin levels compared between baseline and week 48, by treatment groups.

Results. The total cholesterol concentration in rosiglitazone group increased from 5.76 ±1.2 to 7.1±1.6 mmol/l (23% increase, p<0.05), HDL levels increased from 0.91± 0.44 to 1.3± 0.2 (38% increase, p<0.01) and LDL levels increased from 3.5± 0.98 to 4.5± 1.0 (28% increase, p<0.05). Treatment with metformin had no significant effect on total, HDL and LDL cholesterol. After 48 weeks of treatment, the fasting triglycerides concentration in the metformin group declined from 4.1±1.6 to 3.2±1.3 mmol/l (22% decrease, p<0.05) but in the rosiglitazone group no statistically significant effect on plasma triglycerides was noted. Furthermore, after 48 weeks of treatment the fasting insulin concentration in the rosiglitazone group declined by 49% and in the metformin group by 28%. This improvement in insulin secretion could be clearly demonstrated when the sums of insulin concentrations after oral glucose tolerance test were compared: 548±13 to 345±11.8 mIU/l in the rosiglitazone group (37% decrease, p<0.01) and from 552±15 to 420±12 mIU/l in the metformin group (24% decrease, p<0.01).

Conclusions. The study demonstrates that both therapies improve insulin resistance. However, treatment with metformin has no effect on total, HDL and LDL cholesterol, but significantly reduces triglycerides, which has beneficial effect on the lipid status in these patients. Rosiglitazone causes significant increases in total cholesterol, HDL and LDL, but has no effect on triglycerides concentrations.
Introduction

The use of the highly active antiretroviral therapy (HAART) has been associated with a dramatic improvement of morbidity and mortality in HIV-infected patients (1, 2). In recent years, however, concern has been raised by the long-term toxicity of HAART (3). Since the introduction of protease inhibitors (PI) for treatment of HIV infection, metabolic abnormalities (dysregulation of glucose metabolism, dyslipidemia) and morphologic changes (fat accumulation and lipoatrophy) have been extensively reported in treated patients. We are still not able to fully define and understand the exact mechanism and pathogenesis of these metabolic disorders, but association with increased risk of cardiovascular disease is likely to become a significant problem (4, 5).

It is apparent that the effects of PI on glucose and lipid metabolism need to be examined independently of syndromes of fat redistribution (lipodystrophy), which occur in patients who have never been treated with PI (6). Insulin resistance may be considered the first pathogenetic step towards impaired glucose tolerance and, eventually, diabetes mellitus in HIV infected patients, treated with PI containing HAART (7-9). Concerning insulin resistance, dietary interventions and moderate aerobic exercise are accepted as general health measures (14). If a pharmacological intervention is needed, the best choices are probably insulin sensitizing agents like metformin and glitazones (15, 16).

The aim of the present study was to evaluate the effects of insulin sensitizers on lipid metabolism in HIV infected patients receiving PI containing HAART with respect to the improved insulin sensitivity. The effects of two insulin sensitizers, metformin and rosiglitazone, were studied and compared.

Materials and Methods

Study design

In this prospective randomized study, 90 male patients were recruited at the beginning of 2001. The study group consists of 60 Slovenian patients who were treated at the Department of Infectious Diseases in Ljubljana, Slovenia, and 30 American patients who were treated at UCSD in San Diego, USA. Patients were considered eligible on the basis of the following inclusion criteria.
criteria: documented HIV infection, age >18 years, stable PI-containing HAART regimen for at least 12 months prior to the study enrolment, impaired glucose tolerance (IGT) with insulin resistance characterized by fasting insulin concentration greater than 20 mU/L. Eligible patients were randomly assigned to receive either metformin (Aglurab® – Medis) 1g/day (metformin group, n=30) or rosiglitazone maleate (Avandia® – Glaxo Smith-Klein) 4 mg/day (rosiglitazone group, n=30) or no treatment (control group, n=30). All patients were taking one protease inhibitor (indinavir) and two nucleoside analogues (lamivudine, stavudine, zidovudine or didanosine). Clinical examinations and laboratory tests were performed at baseline and after 48 weeks.

Laboratory measurements

Plasma HIV RNA concentrations (HIV viral load) were determined by the Cobas Amplicor HIV-1 Monitor Assay version 1.5 (Roche Molecular Systems, Branchburg, NJ, USA); results below the limit of detection were assigned a value of <20 copies/mL plasma. CD4-lymphocytes counts (CD4 cell count) were measured by three-color flow cytometry and hematology analyzers.

Normal and impaired glucose tolerance were defined according to the American Diabetes Association guidelines-fasting glucose of less than 6.1 mmol/l, 6.1-6.9 mmol/l, respectively, or blood glucose 2 h after glucose-tolerance test (75g) of less than 7.8 mmol/l, 7.8-11.1 mmol/l, respectively. For purposes of clarity, patients with impaired fasting glucose 6.1-6.9 mmol/l were defined as having impaired glucose tolerance. Total cholesterol, LDL, HDL and triglycerides were measured spectrometrically by an Olympus Corp. Analyzer (New Hyde Park, NY, USA). Basal insulin levels were measured by the hexokinase method with an Olympus Corp. Analyzer (New Hyde Park, NY, USA). Basal insulin levels were determined using a commercial radioimmunoassay method- IRMA Biosource Europe S.A. (Nivelles, Belgium).

Fasting total cholesterol, HDL and LDL cholesterol and triglycerides were determined. Patients were considered to have hypercholesterolaemia, low HDL-cholesterol concentration, high LDL-cholesterol concentration or hypertriglyceridaemia, if their plasma measurements were >5.0 mmol/L, <0.9 mmol/mL, >3.0 mmol/L or >2.0 mmol/L, respectively.

Statistical analysis

Data is given as means and standard error of means (SEM). Continuous variables were compared with the t-test. Statistical analysis was performed using the SPSS 10.0 statistical software package. All given p-values are two-tailed and a p-value of < 0.05 was considered to indicate statistical significance.

Results

Patient population

90 male HIV infected patients on PI containing HAART were included in the study and randomly assigned to receive rosiglitazone (n=30), metformin (n=30) or no treatment (n=30). All patients completed 48 weeks protocol. Compliance with the study medication based on pill count was not different between all groups (was similar among the groups). Baseline clinical characteristics of the patients in each treatment group are presented in Table 1. All groups matched for age, BMI and duration of HIV infection. The mean age of study population was 42.3 ± 10.7 years and BMI 24.2 ± 3.1 kg/m². The mean duration of HIV infection was 7.8 ± 2.7 years, while the mean duration of HAART therapy was 3.1 ± 2.1 years.

There were no significant changes in blood counts, viral load or CD4 counts with rosiglitazone and metformin treatment. There were no statistically significant changes in the control group.

Effects on fasting blood lipid levels

Baseline metabolic data and data after 48 weeks of treatment with metformin, rosiglitazone or without treatment are presented in Table 2. Baseline levels of serum triglycerides, total, HDL, and LDL cholesterol did not differ between the two treatment groups, but patients in the control group had higher baseline HDL cholesterol levels compared to the rosiglitazone and metformin groups (p<0.05). After 48 weeks of treatment no significant changes in total, HDL, and LDL cholesterol were found in the metformin group. However, statistically significant increases from baseline were observed in total, HDL and LDL cholesterol levels in the rosiglitazone group. The total cholesterol concentration in the rosiglitazone group increased from 5.76 ±1.2 to 7.1±1.6 mmol/l (23% increase, p<0.05) HDL levels increased from 0.91± 0.44 to 1.3± 0.2 (38% increase, p<0.01) and LDL levels increased from 3.5± 0.98 to 4.5± 1.0 (28% increase, p<0.05). After 48 weeks of treatment, the fasting triglycerides concentration in the metformin group declined from 4.1±1.6 to 3.2±1.3 mmol/l (22% decrease, p<0.05), while in the rosiglitazone group no statistically significant effect on plasma triglycerides was noted.

Total cholesterol/HDL cholesterol ratio and LDL cholesterol/HDL cholesterol ratio did not change significantly in any treatment group.

The analysis also assessed the proportion of patients in each treatment group at the conclusion of the study who had total cholesterol levels greater than 5.0 mmol/
l – the threshold for increased incidence of coronary heart disease in epidemiologic studies. These proportions were 63% in the metformin group, 90% in the rosiglitazone group and 30% among HAART naïve patients. Finally, 12% of patients had a highly atherogenic lipid profile (total cholesterol >6.5 mmol/L, LDL:HDL >4.1, triglycerides >4 mmol/L) at baseline; this profile was found in 20% patients at study end.

**Glycemic control**

Although the mean fasting plasma glucose (FPG) concentrations did not change significantly between the rosiglitazone and metformin groups, they significantly decreased compared with the control group. The mean FPG concentrations in the rosiglitazone group decreased from 6.5±0.22 to 4.5±0.36 mmol/L (P<0.05) and in the metformin group from 6.7±0.12 to 4.3±0.46 mmol/L (P<0.05) compared to the control group (6.6±0.1 mmol/L) (Table 2).

**Effect on fasting insulin levels**

All the study groups had high basal fasting insulin levels exceeding the normal range for the assay (5-20 mIU/L). After 48 weeks of treatment, the fasting insulin concentration in the rosiglitazone group declined from 39.5±7.4 to 20.3±5.4 mIU/L (49% decrease) (p<0.01) and in the metformin group 40.3±5.6 to 29.2±6.4 mIU/L (28% decrease) (p<0.01) (Table 2). This improvement of insulin secretion could be clearly demonstrated when the sums of insulin concentrations after oral glucose tolerance test were compared: 548±13 to 345±11.8 mIU/L (37% decrease) (p<0.01) in the rosiglitazone group and from 552±15 to 420±12 mIU/L in the metformin group (24% decrease) (p<0.01) (Table 2).

**Discussion**

An investigation of 60 male patients in our study who received metformin or rosiglitazone established different effects on serum lipid concentrations associated with each drug; specifically, the changes observed with rosiglitazone therapy produced more pronounced disturbances of lipid levels.

The implications of dyslipidemia in HIV infected individuals are not completely known, but the type, incidence and degree of the abnormalities that are observed with this disease and its treatment may be ex-

<table>
<thead>
<tr>
<th>characteristics</th>
<th>rosiglitazone (n=30)</th>
<th>metformin (n=30)</th>
<th>controls (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>total cholesterol (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>5.76±1.2</td>
<td>6.0±1.3</td>
<td>5.8±1.7</td>
</tr>
<tr>
<td>week 48</td>
<td>7.1±1.6*</td>
<td>5.9±1.58</td>
<td>5.6±1.25</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>0.91±0.44</td>
<td>1.0±0.4</td>
<td>1.3±0.5</td>
</tr>
<tr>
<td>week 48</td>
<td>1.3±0.2**</td>
<td>0.97±0.6</td>
<td>1.2±0.3</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>3.5±0.98</td>
<td>3.36±1.1</td>
<td>3.21±0.91</td>
</tr>
<tr>
<td>week 48</td>
<td>4.5±1.0*</td>
<td>3.4±1.5</td>
<td>3.4±0.8</td>
</tr>
<tr>
<td>triglycerides (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>3.9±1.8</td>
<td>4.1±1.6</td>
<td>3.7±1.3</td>
</tr>
<tr>
<td>week 48</td>
<td>4.2±1.5</td>
<td>3.2±1.3*</td>
<td>3.85±1.2</td>
</tr>
<tr>
<td>fasting glucose (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>6.5±0.22</td>
<td>6.7±0.12</td>
<td>6.6±0.1</td>
</tr>
<tr>
<td>week 48</td>
<td>4.5±0.36*</td>
<td>4.3±0.46*</td>
<td>6.4±0.4</td>
</tr>
<tr>
<td>fasting insulin (mIU/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>39.5±7.4</td>
<td>40.3±5.6</td>
<td>39.7±4.5</td>
</tr>
<tr>
<td>week 48</td>
<td>20.3±5.4**</td>
<td>29.2±6.4**</td>
<td>40.2±5.6</td>
</tr>
<tr>
<td>sum insulin (mIU/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>548±13</td>
<td>552±15</td>
<td>550±10</td>
</tr>
<tr>
<td>week 48</td>
<td>345±11.8**</td>
<td>420±12**</td>
<td>547±11</td>
</tr>
</tbody>
</table>

Data are means ± SEM; *p <0.05 week 48 versus baseline; **p <0.01 week 48 versus baseline; HDL, high density lipoprotein; LDL, low density lipoprotein
Acta Dermatoven APA Vol 14, 2005, No 3

Clinical study Metformin and rosiglitazone in HIV patients

were not preselected on the basis of a specific fat distribution criterion, and peripheral subcutaneous fat was not assessed. In contrast, Gelato et al. demonstrated increased peripheral subcutaneous fat levels in response to rosiglitazone in a small pilot study of HIV-infected patients (27).

Our data suggest that the effects of metformin therapy used in insulin resistant HIV-infected patients are encouraging not only because of the improvement of glucose metabolism but also because of a reduction of fasting triglycerides by 22%. There were no changes in total, HDL and LDL cholesterol in the metformin group. Rosiglitazone has a role in managing insulin resistance and glucose abnormalities, but it disappointed in regard to the lipid metabolism. During the 48 weeks of rosiglitazone treatment, serum total cholesterol, HDL and LDL fractions significantly increased. Results of our study are consistent with prior studies that demonstrated effects of metformin and rosiglitazone on serum lipid levels. Both drugs vary in their ability to affect lipids. Greater reduction of triglycerides in the metformin group than reported in preceding studies may be a result of longer duration of therapy (48 weeks in our study vs. 8 and 12 weeks, respectively) (23, 24). Metformin reduced triglycerides while rosiglitazone did not affect them. Details of the pathophysiological mechanisms of hypertriglycerideremia remain to be clarified. In addition to increasing triglycerides, rosiglitazone also elevated total cholesterol, therefore careful monitoring of serum lipids is mandatory when glitazones are used, especially in patients with pre-existing dyslipidemia. For patients with insulin resistance and lipid abnormalities metformin is a better choice, though it has less of an effect on managing insulin resistance in these patients.

Because of prolonged survival of HIV infected patients, PI-induced development of diabetes mellitus and dyslipidemia is of potential concern, as both disorders are closely associated with an increased risk of cardiovascular disease.

Acknowledgement

This study was supported by the Ministry of Education, Science and Sports, Republic of Slovenia, Trg OF 13, Ljubljana, Slovenia (Research project: J3-3545)

REFERENCES


3. Carr A, Samaras K, Thorsdottir A, Kaufmann GR, Chisholm DJ, Cooper DA. Diagnosis, prediction


AUTHORS’ ADDRESSES

Janez Tomažič, MD, PhD, Dept. of Infectious Diseases and febrile Illnesses, University Medical Centre Ljubljana, Japljeva 2, 1000 Ljubljana, Slovenia

Primož Karner, MD, Dept. of Infectious Diseases and febrile Illnesses, University Medical Centre Ljubljana, Japljeva 2, 1000 Ljubljana, Slovenia

Ludvik Vidmar, MD, PhD, Dept. of Infectious Diseases and febrile Illnesses, University Medical Centre Ljubljana, Japljeva 2, 1000 Ljubljana, Slovenia

Mojca Matičič, MD, PhD, Dept. of Infectious Diseases and febrile Illnesses, University Medical Centre Ljubljana, Japljeva 2, 1000 Ljubljana, Slovenia

Prem M. Sharma, MD, PhD, Dept. of Medicine, Division of Endocrinology and Metabolism, University of California, San Diego, La Jolla, USA

Andrej Janež, MD, PhD, Dept. of Endocrinology, Diabetes and Metabolic Diseases, Medical Centre Ljubljana, Zaloška 7, 1000 Ljubljana, Slovenia