Reduction of glycosilated haemoglobin with stable plasma insulin level in a ph+ cml diabetic patient responsive to imatinib

We recently reported on the improvement of fasting glucose in diabetic chronic myeloid leukaemia (CML) patients treated with imatinib.[1] We here describe a further case on treatment with imatinib, in which we sequentially tested, in addition to the fasting glucose (FG) levels, the glycosilated haemoglobin fraction (Hb A1c) and plasma insulin.

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A 50 year-old woman who presented at our Institution in March 2001 with leukocytosis (70×10^9/L), was diagnosed as having Ph+ CML. Since March 2000 she had been diagnosed type 2 diabetes (median glucose level 280 mg/dl, range 230-320) and was on therapy with an oral antidiabetic drug, with poor glycemic control. Following diagnosis of CML, in April 2001 the patient was started on interferon (IFN-α) and hydroxyurea (HU), reaching a complete haematological response (CHR) after two months and a complete cytogenetic response (CCR) after 6 months of therapy. However, CCR was lost at 27 months (80% Ph+ cells). During IFN therapy, a worsening of FG level was observed (median 320 mg/dL, range 240-395), insulin therapy (40 UI/day) was required and the oral antidiabetic drug discontinued.

Owing to loss of response to IFN, imatinib at the standard dosage of 400 mg/day was started in July 2004; at that time, under insulin dosage of 45 UI/day, median FG level was 320 mg/dL, Hb A1c fraction was 11.5% (normal range 4.5-6.3) and plasma insulin level was 14.5 U/L in the morning and 30.3 U/L two hours after dinner (normal range 5-22 UI/L).

Imatinib was well tolerated and the only adverse effect recorded was weight increment during the first eight weeks of therapy, which was controlled by diuretic therapy. A reduction of FG with respect to the first week was observed at the sixth week (300 mg/dL and 150 mg/dL, respectively) under the same insulin dosage and dietary intake; at that time Hb A1c fraction was 8%. This improvement allowed for a reduction of insulin dosage, especially in the early morning.

At 12 weeks of imatinib therapy the patient obtained again a CCR, as evaluated at conventional cytogenetics (20/20 Ph- cells); Hb A1c fraction was 6.4%, whereas plasma insulin level was in the normal range (22 U/l, morning level). At 18 weeks, plasma insulin level was stable at 14 UI/l and Hb A1c fraction was 5%.

In the last years, imatinib has become the gold standard for treatment for CML;[2] this drug is a selective inhibitor of BCR/ABL tyrosine kinase originating from the derivative Ph chromosome, as well as certain other tyrosine kinases.[3]

Imatinib can be safely administered also in patients with diabetes and heart disease. We recently observed that imatinib may control FG level in diabetic CML patients responsive to therapy,[1] with a mechanism presently unknown. A possible direct role on key enzymes of glucose metabolism pathways was recently evidenced by an *in vitro* experiment performed to assess the proliferative activity of K562 cells under imatinib treatment.[4] In our previous report we hypothesized an indirect role of imatinib, which might act on restoring the peripheral glucose tolerance, which is abnormal in type 2 diabetes, via a possible reduction of free fatty acid concentration (insulin resistance) or, alternatively, through an interference with the molecular mechanism(s) for signalling in diabetic cells (insulin receptor substrate-IRS-pathway).[1]

In the present case, the sequential reduction of Hb A1c fraction and the demonstration of stable insulin plasma levels provide further evidence for an effect of imatinib in increasing insulin sensitivity. In fact, imatinib not only appears to improve the FG level (with a consequent reduction of exogenous insulin in our patient), but also seems to reduce the percentage of glycosilated haemoglobin, that in diabetic patients represents an assessment of the glycemic control during insulin therapy. The mechanism(s) underlying this phenomenon remains unclear, but a possible interference exerted by imatinib on insulin signalling pathways has to be strongly considered.

In conclusion, the present report confirms that imatinib may play a favourable role in glucose metabolism in diabetic patients, and warrants further prospective investigations aimed at investigating the molecular mechanisms of this metabolic effect .

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