CASE REPORT

Dasatinib improves insulin sensitivity and affects lipid metabolism in a patient with chronic myeloid leukaemia

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SUMMARY

A 65-year-old woman had been visiting our department for the treatment of type-2 diabetes mellitus since December 2012. Her glycated haemoglobin levels were well controlled (≈5.8% (40 mmol/mol)) by metformin (500 mg). In July 2014, her white cell count increased suddenly to 33 530 cells/μL and she was diagnosed with Ph+ chronic myeloid leukaemia. She was started on dasatinib (100 mg), which immediately normalised plasma levels of WCC. Dasatinib improved the glycaemic index to <6.0% and also improved plasma levels of triglycerides (TGs) and high-density lipoprotein-cholesterol (HDL-c). Levels of low-density lipoprotein-cholesterol were increased but remained within the normal range. The TG:HDL-c ratio and Quantitative Insulin Sensitivity Check Index rapidly improved. Followed by an improvement in insulin sensitivity, plasma levels of adiponectin and leptin were increased. This case study suggests that dasatinib might have positive as well as negative effects on the metabolism of glucose and lipids.

BACKGROUND

Introduction of small tyrosine kinases (TKIs) has improved survival in patients with chronic myeloid leukaemia (CML). Imatinib is a small-molecule TKI used in CML treatment, and it improves insulin sensitivity.[1] Dasatinib is also a breakpoint cluster region protein/Abelson murine leukaemia viral oncogene homolog-l and proto-oncogene tyrosine-protein kinase Src family TKI.[2] However, the effect of dasatinib on the metabolism of glucose and lipids is not known. We report a case of a patient with concurrent CML and type-2 diabetes mellitus (T2DM), in whom we estimated insulin sensitivity and lipid metabolism.

CASE PRESENTATION

A 65-year-old woman had been receiving T2DM treatment from our department since December 2012. Glycated haemoglobin $(Hb)_{A1c}$ levels were well controlled (≈5.8% (40 mmol/mol)) by metformin (500 mg). In July 2014, the patient's white cell count increased suddenly to 33 530 cells/μL; basophils (7.5%) and Hb_{A1c} (6.2% (44 mmol/mol)) were also elevated slightly (table 1). Plasma levels of vitamin B_{12} were higher (1450 (180–914) pg/mL) and the neutrophil alkaline phosphatase score was low (136 (188.5–367.0)). We suspected CML and consulted a haematologist. Chromosome staining by G-banding (46, XX, t [9;22] [q34;q11.2]) on bone-marrow examination prompted a diagnosis of Ph+ CML. In August 2014, the patient was started on dasatinib (100 mg).

OUTCOME AND FOLLOW-UP

Dasatinib immediately normalised the plasma levels of WCCs (8200, 8470 and 33 530 cells/μL at 12, 5 and 1 month before treatment; 4800, 5960, 5990 and 5220 cells/μL at 1, 3, 4 and 10 months after treatment, respectively). After introduction of dasatinib, metformin therapy (500 mg per day) for T2DM was continued and glycaemic control was stable with no hypoglycaemic symptoms (5.9% (41), 5.8% (40) and 6.2% (44 mmol/mol) at 12, 5 and 1 month before treatment; 5.6% (38), 5.6% (38), 5.9% (41) and 5.8% (40 mmol/mol) at 1, 3, 4 and 10 months after treatment, respectively) (table 2). Plasma levels of low-density lipoprotein-cholesterol (LDL-c) were increased slightly but remained within the normal range (72.0, 99.0 and 61.8 mg/dL at 12, 5 and 1 month before treatment; 98.0, 90.0, 106.8 and 116.4 mg/dL at 1, 3, 4 and 10 months after treatment, respectively). Plasma levels of triglycerides (TGs) were decreased (176, 174 and 266 mg/dL at 12, 5 and 1 month before treatment; 75, 105, 176 and 148 mg/dL at 1, 3, 4 and 10 months after treatment, respectively) (table 2). In accordance with these data, plasma levels of high-density lipoprotein-cholesterol (HDL-c) were immediately (but temporally) increased (48, 43 and 32 mg/dL at 12, 5 and 1 month before treatment; 49, 49, 42 and 31 mg/dL at 1, 3, 4 and 10 months after treatment, respectively). The TG:HDL-c ratio as well as the Quantitative Insulin Sensitivity Check Index (QUICK-I) are markers for insulin resistance.[3 4] The TG:HDL-c ratio was immediately (but temporally) improved (3.7, 4.1 and 8.31 at 12, 5 and 1 month before treatment; 1.53, 2.14, 4.19 and 4.77 at 1, 3, 4 and 10 months after treatment, respectively). Similarly, QUICK-I was immediately (but temporally) improved (0.36 and 0.34 at 5 and 1 month before treatment; 0.38, 0.36, 0.34 and 0.34 at 1, 3, 4 and 10 months after treatment, respectively) (table 2). Followed by improvement in markers of insulin sensitivity (TG:HDL-c and QUICK-I), plasma levels of adiponectin increased as compared with before treatment (4.9 μg/mL at 1 month before treatment; 6.2, 9.4, 9.9 and 7.8 μg/mL at 1, 3, 4 and 10 months after treatment, respectively). In accordance with change in body weight (50.0, 49.0 and 49.0 kg at 12, 5 and 1 month before treatment; 50.0 50.0, 50.5 and 49.8 kg at 1, 3, 4 and 10 months after treatment, respectively), plasma levels of leptin were increased

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Table 1 Laboratory findings at diagnosis

Blood		Biochemistry		Metabolism	
WCC	**33 530** /μL	TP	7.1 g/dL	Glucose	115 mg/dL
RBC	535 ×10^4/μL	Alb	4.6 g/dL	IRI	6.9 μU/mL
Hb	14.6 g/dL	CK	19 IU/L	Hb_{A1c}	6.2 %
Hct	44 %	AST	20 IU/L	T Chol	147 mg/dL
MCV	82.2 fL	ALT	10 IU/L	TG	**266** mg/dL
MCH	27.3 pg	LDH	471 IU/L	HDL-c	32 mg/dL
Plt	**66.3** ×10^4/μL	ALP	179 IU/L		
Ret	2.14 %	γ GTP	16 IU/L		
		AMY	109 IU/L	Other	
Blast	**0.5** %	Cre	0.47 mg/dL	ALP (NAP) Score	
Myelocyte	**6** %	BUN	17.6 mg/dL	Type0	38 %
Metamyelocyte	**2** %	Na	143 mEq/L	Type1	10 %
Stab	4 %	K	4.6 mEq/L	Type2	31 %
Seg	58.5 %	Cl	107 mEq/L	Type3	20 %
Neut	62.5 %	Ca	9.9 mg/dL	Type4	1 %
Mono	3 %	Pi	4 mEq/L	Type5	0 %
Lymp	17 %	Fe	85 μg/dL	Positive ratio	**62** %
Eosino	1.5 %	UIBC	314 μg/dL	SCORE	**136**
Baso	**7.5** %	Ferritin	17.4 ng/mL		
Erythroid	**0.5** %			Vitamin B12	**1450** pg/mL

Bold letters denote abnormal values.
Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMY, amylase; AST, aspartate aminotransferase; Baso, basophil; BUN, blood urea nitrogen; BW, body weight; CK, creatine kinase; Cre, creatinine; Eosino, Eosinophil; GTP, glutarmyltranspeptidase; Hb, haemoglobin; Hb_{A1c}, glycated haemoglobin; Hct, hematocrit; IRI, immunoreactive insulin; LDH, Lactate dehydrogenase; Lymp, Lymphocyte; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; Mono, Monocyte; NAP, neutrophil alkaline phosphatase; ND, not determined; Neut, ; Plt, platelet count; RBC, red blood cells; Ret, reticulocyte count; Seg, segmental neutrophil; T Chol, total cholesterol; TG, triglyceride; TP, total protein; UIBC, unsaturated iron binding capacity; WCC, white cell count;

(7.9 ng/mL at 1 month before treatment; 7.1, 9.9, 10.1 and 6.6 ng/mL at 1, 3, 4 and 10 months after treatment, respectively) (table 2).

DISCUSSION

Imatinib is known to improve glucose metabolism. How TKIs improve glucose metabolism has been previously studied.[1 5] The effect of imatinib is thought to be due to the improvement of the secretion of, and sensitivity to, insulin.[5] The effect of imatinib on insulin secretion is thought to be due to apoptosis of β-cells in pancreatic islets via increased activation of nuclear factor-κ B.[6] Imatinib has been shown to reverse T1DM in non-obese diabetic mice.[7] Improvement in insulin sensitivity has been reported to be due to inhibition of tumour necrosis factor-α production and inhibition of endoplasmic reticulum stress.[8 9] Moreover, a recent report suggested that imatinib improves insulin sensitivity through increased levels of adiponectin in plasma.[1] Another study demonstrated that imatinib promotes adipocyte differentiation from multipotential mesenchymal stromal cells by suppression of platelet-derived growth factor-induced PI3 kinase, and that an increase in numbers of adipocyte cells contributes to an increase in adiponectin levels in plasma.[10] In accordance with those studies, improvement in plasma levels of adiponectin and leptin were followed by

Table 2 Clinical course

	Before 12 months	Before 5 months	Before 1 month	After 1 month	After 3 months	After 4 months	After 10 months
BW (kg)	50	49	49	50	50	50.5	49.8
WCC (/μL)	8200	8470	33 530	4800	5960	5990	5220
Basophil (%)	ND	ND	7.5	0.6	ND	0.2	0.2
Basophil (/μL)	ND	ND	2515	29	ND	12	10
Hb_{A1c} (%)	5.9	5.8	6.2	5.6	5.6	5.9	5.8
Fasted plasma glucose (mg/dL)	84	101	115	99	104	113	102
Fasted IRI (μU/mL)	ND	5.8	6.9	4.3	5.4	8.1	9.1
QUICK-I	ND	0.36	0.34	0.38	0.36	0.34	0.34
T Chol (mg/dL)	155	177	147	162	160	184	177
TG (mg/dL)	176	174	266	75	105	176	148
HDL-c (mg/dL)	48	43	32	49	49	42	31
LDL-c (mg/dL)	71.8	99.2	61.8	98	90	106.8	116.4
TG/HDL-c	3.7	4.1	8.3	1.53	2.14	4.19	4.77
Adiponectin (μg/mL)	ND	ND	4.9	6.2	9.4	9.9	7.8
Leptin (ng/mL)	ND	ND	7.9	7.1	9.9	10.1	6.6

BW, body weight; HDL-c, HDL cholesterol; Hb_{A1c}, glycated haemoglobin; IRI, immunoreactive insulin; LDL-c, LDL cholesterol; QUICK-I, Quantitative Insulin Sensitivity Check Index; T Chol, total cholesterol; TG, triglyceride; WCC, white cell count.

improvement in insulin sensitivity in our patient. Those studies suggested that the time difference between an increase in insulin sensitivity and adiponectin levels were due to the time taken for the proliferation and development of adipocytes. Taken together, it appears that the PDGF receptor is a common target for imatinib and dasatinib,[11] and that the improvement in insulin sensitivity elicited by dasatinib may be due to a mechanism similar to that of imatinib.

In our patient, dasatinib immediately (and continuously) improved plasma levels of TGs and HDL-c. In contrast, plasma levels of LDL-c increased gradually. In accordance with our data, Rea *et al*[12] reported that nilotinib improves plasma levels of TG, HDL-c and LDL-c. In contrast, Gottardi *et al*[13] reported that imatinib decreases plasma levels of LDL-c. Considering that change in the TG:HDL-c ratio was reciprocally consistent with that of QUICK-I, improvement in plasma levels of TG and HDL-c in our patient was probably due to increased insulin sensitivity in the peripheries. However, why plasma levels of LDL-c were increased in our patient is not clear. Hence, if TKIs are administered in patients with hypercholesterolaemia, careful follow-up of plasma levels of LDL-c should be considered.

Learning points

- Dasatinib may temporally improve insulin sensitivity and plasma levels of TGs and high-density lipoprotein-cholesterol.
- Dasatinib may increase plasma levels of low-density lipoprotein-cholesterol.
- The metabolism of glucose and lipids might need to be monitored in patients treated with dasatinib.

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Competing interests None declared.

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