CASE REPORT

Sunitinib and improved diabetes control

Helen Elizabeth Jane Tyrrell, Thinn Pwint

Department of Oncology,
Buckinghamshire NHS Trust,
Aylesbury, Buckinghamshire,
UK

Correspondence to

Dr Helen Elizabeth Jane Tyrrell,
helen_ej_tyrrell@yahoo.com

Accepted 6 December 2014

SUMMARY

There is increasing use of tyrosine kinase inhibitors as targeted therapy for several malignancies. Sunitinib is the first-line treatment for renal cancer and we report a case of a man receiving this medication who also had diabetes. When started on sunitinib he experienced improvement in his diabetes control with reduction in his insulin requirements, which later worsened when sunitinib was reduced or stopped. Several retrospective studies have been performed demonstrating this effect with sunitinib, but to date no prospective studies have been reported. Most tyrosine kinase inhibitors reduce blood glucose levels in diabetics, but some agents, such as nilotinib, may increase them. There is no consensus on the mechanism of action of sunitinib in reducing glucose levels. Several theories have been postulated, such as increased insulin secretion, increased insulin sensitivity, reduced loss of islet cells, the gastrointestinal side effects of sunitinib, or an interaction with other antihyperglycaemic agents.

BACKGROUND

Tyrosine kinase inhibitors (TKIs) are a targeted cancer therapy that interferes with the action of enzymes, namely tyrosine kinases, which are involved in cancer growth factor signalling and angiogenesis. Sunitinib is the first-line treatment for metastatic renal cell cancer. Sunitinib is an inhibitor of vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR); these are often overexpressed in renal cell cancer and this leads to tumour angiogenesis and growth.¹ It is given in 6-week cycles, with 4 weeks of treatment followed by 2 weeks without.¹ As well as being used in renal cancer, TKIs are also used against pancreatic neuroendocrine tumours, gastrointestinal stromal tumours and leukaemias.² Other TKIs include sorafenib, imatinib, pazopanib and nilotinib. These can have effects on glucose metabolism, causing either increases or decreases in blood sugars, though their mechanisms are currently not clear.²

CASE PRESENTATION

A 61-year-old man presented in 2008 with lethargy and weight loss. Subsequent blood tests showed anaemia and hypercalcaemia. A CT scan revealed a right sided renal tumour, retrocaval, hilar and aortopulmonary lymphadenopathy and pulmonary nodules, without bone metastases. He underwent a right nephrectomy and histology showed a G4pT3b clear cell tumour with positive resection margins. A few months later repeat CT showed new liver lesions and sunitinib 50 mg once daily was started in April 2009.

The patient had an extensive medical history with chronic pancreatitis, type II diabetes on

insulin, myocardial infarction and hypertension. In January 2009, prior to starting sunitinib, his diabetes was controlled with mixtard 30 insulin: 34 units in the morning and 30 in the evening. He had generally erratic sugars and his glycated haemoglobin (HbA1c) was elevated at 55 mmol/mol: this was actually lower than was typical for him (likely due to a prolonged intensive therapy unit stay following his nephrectomy), as readings in 2008 had been 69 mmol/mol and 79 mmol/mol. On review by the diabetes team in July 2009, 4 months after starting sunitinib, his HbA1c was down to 49 mmol/mol, and his insulin mixtard had been reduced to sixteen units twice daily (figure 1).

Sunitinib was temporarily stopped in September 2010 as the patient developed grade 3 mucositis, and subsequently restarted at a lower dose of 37.5 mg once daily after 2 weeks; he tolerated this well. His blood sugars rose slightly with the dose reduction: HbA1c readings had been 43–48 mmol/mol earlier in 2010, but in January 2011 his HbA1c was 52 mmol/mol. At this point he was taking Humalog mix 25 four units twice a day for his diabetes, mixtard being no longer produced.

In December 2012, his sunitinib was reduced further to 25 mg daily due to recurrence of mucositis and hand-foot syndrome; at this point his HbA1c rose, with readings of 54–55 mmol/mol. At no point with sunitinib did he suffer from anorexia or fatigue, he remained active throughout his treatment with this medication. In early 2013 there was disease progression on the CT with worsening lymphadenopathy and the patient was feeling progressively more tired. Therefore, sunitinib was stopped. At this point his blood sugar levels began to increase, with his HbA1c rising to 68 mmol/mol and his Humalog was increased to seven units in the morning and eight units in the evening.

OUTCOME AND FOLLOW-UP

In April 2013, axitinib 5 mg twice daily was started and the patient's blood sugar levels improved again with an HbA1c in July of 62 mmol/mol, though the axitinib was soon decreased to 3 mg twice daily due to diarrhoea and fatigue.

In January 2014, axitinib was stopped due to pulmonary disease progression, at this time HbA1c was significantly higher at 82 mmol/mol (figure 1). The patient was then started on everolimus, but developed rapidly progressive disease and passed away soon afterwards.

DISCUSSION

There have been two retrospective reviews studying blood glucose control in patients with metastatic renal cancer treated with sunitinib. Jong Jin Oh

CrossMark

To cite: Tyrrell HEJ, Pwint T. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-207521

Figure 1 Graph demonstrating glycated haemoglobin (HbA1c) measurements over time as medications were altered.

*et al*³ examined the records of 48 patients in this category, diabetic as well as non-diabetic. There were no type 1 diabetics. 10 out of the 48 patients were type 2 diabetics and were found to have a significant reduction in blood glucose after 2 weeks of sunitinib treatment, but this rebounded in the 2-week off treatment period. The reduction in blood glucose after sunitinib treatment was 76.1 mg/dL, or 41.1% of their initial blood glucose. The rebound was of a smaller magnitude, an increase of 21.9 mg/dL or 20.1%. One of these patients was able to stop treatment for diabetes altogether and a further three patients to reduce their antihyperglycaemic doses. However, though blood glucose levels did change in the 38 non-diabetic patients, the reduction of 6.7 mg/dL and rebound increase of 2.5 mg/dL off treatment did not reach statistical significance.

Billemont *et al*⁴ retrospectively studied glucose levels of 19 patients with type 2 diabetes receiving sunitinib for metastatic renal cell cancer. During the 4 weeks of treatment all 19 patients had a reduction in their blood glucose level, with a mean decrease of 1.77 mmol/L, followed by an average rebound of 0.93 mmol/L during the 2 week rest period. After 2 cycles two patients were able to stop their antihyperglycaemic medications during the treatment phase of the cycle and reinstate them during the rest period. In nine non-diabetic control patients receiving sunitinib, a non-significant reduction in blood glucose was seen, with no variation in levels during the 2 week off treatment period.⁴

There is a case report of long term remission of type I diabetes in a patient treated with sunitinib.⁵ The 64-year-old man was diagnosed with metastatic renal cell cancer in 2003 and underwent interferon- α therapy followed by investigational vaccination treatment. Type 1 Diabetes was diagnosed during the vaccination treatment due to elevated glutamic acid decarboxylase (GAD) antibodies and basal-bolus insulin was started. Later that year, the vaccinations were stopped due to progression and a few months later sunitinib was started. During sunitinib treatment insulin was tapered off and stopped. When sunitinib was stopped in 2007, the patient's glucose remained normal without insulin at the time of publication in 2008. While his diabetes

could have been triggered by the vaccination treatment and recovery caused by it being stopped, the authors attributed the recovery to sunitinib, as anti-GAD antibodies continued to be elevated 15 months after the vaccinations had been stopped.⁵

As well as sunitinib, many other TKIs also have an effect on blood glucose control in patients with diabetes. These drugs have varying levels of activity against the different tyrosine kinase enzymes. Therefore, they have different effects on glucose metabolism: imatinib, dosatinib, sunitinib, sorafenib and pazopanib more commonly reduce blood glucose, but nilotinib normally increases it.² Sunitinib has activity against VEGFR, PDGFR, FMS-like tyrosine kinase 3, BRAF, colony-stimulating factor type I, RET and c-KIT.^{3,4} Imatinib, dosatinib and nilotinib all have activity against BCR-ABL. However, nilotinib is more selective for this target, whereas dasatinib also inhibits SRC kinases.⁶ All three also inhibit PDGFR.⁶

Agostino *et al*⁷ retrospectively analysed blood glucose levels in patients receiving sunitinib, sorafenib, imatinib or dasatinib for all types of malignancy. They found reductions in blood glucose with all four medications. However, their results differed from those trials examining only sunitinib, as they concluded that the magnitude of reduction in blood glucose was similar in diabetic and non-diabetic patients.

The mechanism by which TKIs affect blood glucose is unknown, but there are several theories. Most of these have been studied more extensively for imatinib than for sunitinib, as this medication has been used for longer.

First, it has been suggested that sunitinib may reduce blood glucose through gastrointestinal side effects such as reducing appetite and diarrhoea. However, this is unlikely to be the sole factor in reducing blood glucose levels, as patients receiving sunitinib who had a reduction in blood sugar did not also lose weight, which would be expected if this were the case. In the 2012 study by Jong Jin Oh *et al*,³ BMI reduced by 0.68 in patients with diabetes and 0.25 in non-diabetics; this was not considered a significant change.

A second idea is that sunitinib increases insulin production from β -cells. SRC kinase activity reduces insulin secretion by

human β cells, possibly through the production of reactive oxygen species.⁶ Several TKIs act against SRC-kinases and therefore should enhance insulin release.⁶ A case report by Ono *et al*,⁶ describes a man with chronic myeloid leukaemia (CML) treated with dasatinib, who required 20 units of insulin prior to this treatment, but only needed glimepiride once dasatinib was started. The patient's C peptide levels increased with dasatinib, suggesting it increased endogenous insulin production. However, it was unclear if the improvement in glycaemic control was entirely due to dasatinib, as the patient had also started iron-chelating agents for suspected haemochromatosis during the same admission.

Third, sunitinib may reduce peripheral insulin resistance, possibly via interfering with the insulin-like growth factor 1 (IGF-1) pathway.³ Research giving diabetic rats imatinib found that they had improved insulin sensitivity and glucose disposal rates.⁶ However, in the 2008 study by Billemont *et al*, IGF-1 levels were monitored in five of the patients with diabetes treated with sunitinib: while a decrease was observed at week 4, this was not considered significant.⁴

A fourth mechanism is that sunitinib may prevent β -cells undergoing apoptosis or lead to capillary regression in pancreatic islets. Capillary regression would be due to inhibition of VEGFR and has been observed in mice given a TKI.⁴ Sunitinib inhibits the effect of the c-KIT tyrosine kinase and c-KIT has been reported to increase β -cell survival.³ One study used an animal model to show that imatinib prevents apoptosis of β -cells, thus improving diabetes. This is thought to be due to its action on PDGFR: sunitinib also inhibits this receptor.⁸ Another study looking at imatinib found that this agent activated nuclear factor kappa B via inhibition of c-ABL, and this also protected human β cells from chemical induced apoptosis in vitro.⁶ However, nilotinib also inhibits c-ABL and PDGFR, and this agent increases glucose levels, suggesting this mechanism cannot be the main cause of reduced glucose levels with sunitinib.

A fifth theory is that sunitinib interacts with medications used to control diabetes, leading to hypoglycaemia. This would explain why the reduction in blood sugar is greater in diabetics than patients without diabetics in the two studies looking at sunitinib alone.^{3 4}

Finally, the worsening or improvement of a patient's underlying disease may alter his or her glucose metabolism.⁶

However, it is most likely that the effect of sunitinib on glucose control is due to a combination of the above factors, or a result of another mechanism as yet unknown. A further complicating factor is that the same TKI may have opposing actions on glucose control. Though sunitinib is more often reported as causing hypoglycaemia, there have been cases describing hyperglycaemia with sunitinib.

All the studies published so far investigating glucose control with TKIs have been retrospective. Most of the blood glucose measurements in these studies were random, rather than fasting.³ The next stage would be to undertake prospective

studies of this effect. This also raises questions about whether these drugs could be used as a novel treatment for diabetes.

For the present, it is sensible to monitor diabetic patients starting these medications carefully. It is also recommended that patients be educated to recognise the symptoms and signs of hypoglycaemia and hyperglycaemia and that patients with diabetes regularly self-monitor their blood glucose.² One paper suggests that even in patients without diabetes it is sensible to measure fasting plasma glucose before initiating treatment, every 2 weeks for the first month and monthly thereafter.² An agent's effect on glucose control could also be considered when selecting a TKI with which to treat a patient.

Learning points

- ▶ Tyrosine kinase inhibitors can affect blood glucose control in patients with diabetes.
- ▶ Sunitinib usually leads to a reduction in blood glucose levels.
- ▶ All patients with diabetes being started on these agents should have careful assessment of their diabetes control as they may require alterations in their antihyperglycaemic medication.
- ▶ The mechanism of action for this effect is not entirely understood. Possibilities include increased insulin production, increased β -cell survival, improved peripheral insulin sensitivity, the gastrointestinal side effects of sunitinib, or an interaction between sunitinib and antihyperglycaemic agents.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Motzer RJ, Hutson TE, Tomczak P, *et al*. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *NEJM* 2007;356:115–24.
- 2 Verges B, Walter T, Cariou B. Effects of anti-cancer targeted therapies on lipid and glucose metabolism. *Eur J Endocrinol* 2014;170:R43–55.
- 3 Oh JJ, Hong SK, Joo YM, *et al*. Impact of sunitinib treatment on blood glucose levels in patients with metastatic renal cell carcinoma. *JCO* 2012;42:314–17.
- 4 Billemont B, Medioni J, Taillade L, *et al*. Blood glucose levels in patients with metastatic renal cell carcinoma treated with sunitinib. *Br J Cancer* 2008;99:1380–2.
- 5 Templeton A, Brändle M, Cerny T, *et al*. Remission of diabetes while on sunitinib treatment for renal cell carcinoma. *Ann Oncol* 2008;19:824–5.
- 6 Ono K, Suzushima H, Watanabe Y, *et al*. Rapid amelioration of hyperglycaemia facilitated by dasatinib in a chronic myeloid leukaemia patient with type 2 Diabetes Mellitus. *Intern Med* 2012;51:2763–6.
- 7 Agostino NM, Chinchilli VM, Lynch CJ, *et al*. Effect of the tyrosine kinase inhibitors (sunitinib, sorafenib, dasatinib, and imatinib) on blood glucose levels in diabetic and nondiabetic patients in general clinical practice. *J Oncol Pharm Practice* 2010;17:197–202.
- 8 Louvet C, Szot GL, Lang J, *et al*. Tyrosine kinase inhibitors reverse type 1 diabetes in nonobese diabetic mice. *PNAS* 2008;48:18895–900.

Copyright 2014 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow