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Case Report

Thrombocytopenia: Could it be Vildagliptin

Ahmed Imran Siddiqi[1], Komal Saad[2]

[1]Department of Diabetes and Endocrinology Newham University Hospital, London, UK

[2]Foundation University Medical College, Islamabad. Pakistan

***Corresponding author:** Ahmed Imran Siddiqi, Department of Diabetes and Endocrinology, University College London Hospital, 3rd floor, 250 Euston Road, London.UK. NW1 2PG, E-mail: Aims125@hotmail.com

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Introduction

DPPIV (dipeptidyl peptidase 4) inhibitors have been very effective in improving glycemic control over previous decade. These agents inhibit action of enzyme DPP IV and prolong life of naturally produced GLP 1 (Glucagon like peptide 1) to improve glycemic control in diabetic patients. Sitagliptin was first agent licensed in 2006 and subsequently license was granted to more agents Vildagliptin (2007), Saxagliptin (2009), Linagliptin (2011) [1]. We present here a case of thrombocytopenia in a patient using Vildagliptin.

GLP-1 and GIP are two important incretins studied in human and animal studies. Incretins are produced naturally in gastrointestinal system and increase insulin secretion from beta cells in a glucose dependent manner. Incretins are believed to be responsible for producing 50-70 % of post meal insulin. Once produced in gastrointestinal system GLP-1 has a very short half-life (1-2 minutes) and DPP IV enzyme breaks it down. In addition to increase in insulin production GLP-1 is believed to help increase beta cell number by helping their proliferation and preventing their apoptosis. This two-fold beneficial effect of GLP-1 on beta cells makes medications expected to increase duration of GLP-1 function very attractive. The beneficial effects of beta cell proliferation also suggest earlier use of DPP IV inhibitors in treatment of type 2 DM (Diabetes mellitus). GLP-1 also helps with early satiety, reduced gastrointestinal motility and delayed gastric emptying, reduced hepatic gluconeogenesis and reduction in glucose dependent glucagon production. All these effects help reduce oral intake, improved insulin production, delayed gastric emptying and blunted blood glucose peaks after meals.

Focus was shifted to development of GLP-1 inhibitors as GIP on its own does not show promising effects on glucose control. GIP either did not help at all in glucose metabolism or had some detrimental effects. DPP IV inhibitors were initially introduced as third line agents in treatment algorithm of type 2 DM patients. Their weight neutral effects, decent glycemic control and low risk of hypoglycaemia have proved these agents a decent second line agent in treatment of type 2 DM. All these agents are generally well tolerated. Thrombocytopenia development with use of one of these agents may suggest certain features unique to this agent and not to this class of agents, leading to this specific effect.

Case Report

58 years old lady diagnosed with Type 2 Diabetes Mellitus (DM) 12 years ago, noticed a decline in her platelet count over a year during her routine follow up appointments in Diabetes clinic. Her RBC (red blood cells) and WBC (white blood cells) remained unaffected. She did not experience any untoward effects of low platelet count as she did not have spontaneous bleeding, bruising or excessive bleeding following minor trauma. She was diagnosed with Type 2 DM at age 46 and was initially managed with life style measures. Pharmacological treatment began with Metformin a couple of years later followed by introduction of Glimipride a year later in view of worsening glycemic control. Vildagliptin was the third oral agent introduced as Vildagliptin/Metformin combined pill about four years age with favourable improvement in glycemic control (Table 1). Her eye screening and urine ACR showed no features of microvascular complication. She was also taking Co-renitec (Enalapril maleate &Hydrochlorothiazide) once a day (OD), Simvastatin 40 mg OD and Adcal D3 one tablet twice a day. Hypertension for previous 27 years, pollen hypersensitivity and hypercholesterolemia complete her past medical history. She never smoked, never drank alcohol and did not use any herbal or over the counter medications. Her diet did not change recently and did not include specific traditional foods. She was not allergic to any medications or food.

	Time 0	21 months	27 months	31 months	36 months	45 months
WBC (x106L)	9200		8600			5900
RBC (m/106L)	4.76		4.51			4.61
Hemoglobin (g/dl)	14.33		13.1			13.1
HCT %	41.8		39			41.4
Platelets (x106L)	155,000	114,000	78,000	139000	163000	167000
Neutrophils	50%		44%			49
Lymphocytes	36%		46%			43
Monocytes	8%		5%			6
Eosinophils	6%		5%			2
Basophils	0%		0%			0
HbA1c %		7.1	6.8	8.6	7.4	7.3
Comments	Vildagliptin started		Vildagliptin stopped	Sitagliptin started		

Table 1: Laboratory investigations.

Clinical examination on multiple clinic visits did not find any abnormal signs especially, lymph nodes, spleen or liver were not palpable. Repeated platelet counts on the same analyser, on a different analyser and blood film examination confirmed a gradual but slow decline in platelet counts over a year. Haematologist planned to perform bone marrow biopsy to find out a possible cause for this dropin platelet count. Since there had not been much change in her medications and lifestyle over previous year Vildagliptin stood out as the only intervention prior to her thrombocytopenia. Following discussions among her Diabetologist, Pharmacist and Haematologist Vildagliptin was discontinued once her platelet count dropped to 78000 x 106/L. Within four weeks of discontinuation the platelet counts started to rise which over time got back to usual range Table 1. Bone marrow biopsywasnot performed.

She was then commenced on Sitagliptin to improve her glycemic control four months later with cautious monitoring of platelet counts. This time the counts remained well and continued this way 14 months after commencement of Sitagliptin.

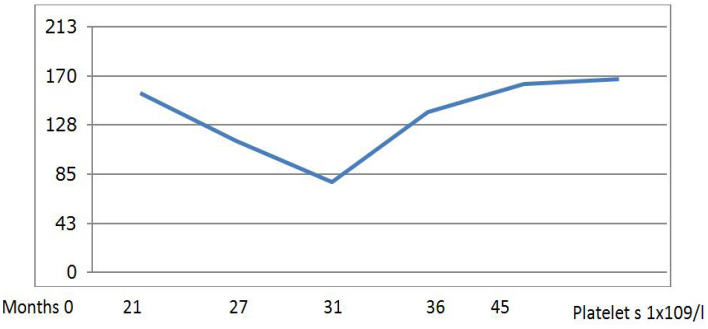

Fig 1: Platelet count changes over time.

Learningpoints

Consider DPP IV inhibitors (Vildagliptin) as a possible cause of low platelet counts although, this is the only case reported so far and does not confirm the causative association.

Discussion

This case suggests an association between Vildagliptin use and gradual decline in platelet count. Platelet count nearly halved after 21 months Vildagliptinuse and gradually improved to normal range a year after its discontinuation. Sitagliptin, another DPP 4 inhibitor was used with cautious monitoring of platelet counts which remains un-affected for more than a year use. The gradual decline in platelet count over many months and rapid improvement following Vildagliptin discontinuation makes this the most likely cause. In presence of another cause of thrombocytopenia platelet count is unlikely to rise and stay stable following Vildagliptin discontinuation. Gradual decline over many months without any systemic symptoms and signs makes viral infections or parasitic infestation as possible cause of thrombocytopenia very unlikely. Slowly developing haematological disorders (myelofibrosis etc) are also very unlikely to completely reverse with normalisation of platelet counts.

We could not find a human case of thrombocytopenia reported associated with Vildagliptin use in literature. Animal studies have shown a possible association between DPP-8/ DPP-9 inhibitors and thrombocytopenia. In a study by Lankas et al. [2], the selective DPP-8/ DPP-9 inhibitor had IC50 values of 30 000, 38 and 55 nM for DPP-4, DPP-8 and DPP-9 respectively. When given to rats for 2 weeks, it was well absorbed (Cmax at 100 mg/kg/day ¼

36.5 mmol/l, area under the curve ¼ 278 mmol/l/h) and it is likely that chronic and profound inhibition of both DPP-8 and DPP-9 ensued. At or below the highest dose tested, the selective DPP-8/DPP-9 inhibitor produced alopecia, thrombocytopenia, reticulocytopenia, splenomegaly and mortality (2/10 rats). Furthermore, in a 2-week study in mice, a dose of 300 mg/kg/day caused death in 12/12 mice. A nonspecific inhibitor (IC50 values of 460, 220 and 320 n/M for DPP-4, DPP-8 and DPP-9 respectively) elicited a toxicity profile in rats similar to that of the DPP-8/DPP-9 selective inhibitor, with an additional finding of anaemia. In a selected group of mice who had their DPP IV gene deleted but retained DPP-8/DPP-9 gene had similar side effects as observed with use of non-selective inhibitors and selective DPP-8/DPP-9 inhibitors. This confirmed that only DPP-8 /DPP-9 inhibition was responsible for alopecia, thrombocytopenia, reticulocytopenia, splenomegaly and mortality; DPP IV inhibition did not contribute to these effects. The beneficial effects on glycemic control are manifested by DPP IV inhibition hence, selective inhibition of DPP IV and no effect on other members of DPP enzyme family is essential to use such medications safely in clinical practice. It is also interesting to note that DPP IV enzyme has an extra cellular catalytic domain however both DPP-8 and DPP-9 are cytosolic. Compounds should be able to get to cytosol to cause DPP-8 and DPP-9 mediated adverse effects [2].

Vildagliptin is believed to effectively inhibit DPP-8/DPP-9 enzymes at high concentrations. In a study Burkey et al [3] in vitro studied the effect of vildagliptin on the activity of recombinant human DPP-4, DPP-8 and DPP-9. Vildagliptin was much more potent at inhibiting DPP-4 than DPP-8 or DPP-9; however, at high concentrations, nearly complete inhibition of each of the enzymes was observed. The KI values for DPP-4, DPP-8 and DPP-9 were 3, 810 and 95 n/M respectively. Previous studies overwhelmingly suggested adverse effects of thrombocytopenia, alopecia, multi organ toxicities and mortality due to DPP-8 DPP-9 inhibitors' inhibition. It is interesting to note that this study did not notice these effects despite complete inhibition of DPP-8 and DPP-9 by Vildagliptin. Brandt et al. conducted detailed studies on Vildagliptin and found it to be selective, potent and bioavailable antihyperglycaemic agent. In selectivity studies they noticed that the IC50 of Vildagliptin for DPP IV was in the 100 n/M range, irrespective whetherpurified DPP IV, human EDTA-plasma or Caco2-cell homogenates were used. OnlyDPP-8 was inhibited in this in vitro selectivity screening (IC50 of 9.0 +/- 0.1 m/M); the activity of DPP II, prolyl oligopeptidase, aminopeptidase P and aminopeptidase N was not significantly affected by Vildagliptin in the 0.1-1 mM concentration range [4]. Is it possible for Vildagliptin to inhibit DPP-8/DPP-9 receptors at therapeutic concentration in some patients resulting in thrombocytopenia? The suggestion of inhibition of DPP-8 DPP-9 by Vildagliptin proved in these studies may suggest this a possibility. There have been only a few anecdotes of thrombocytopenia with Vildagliptin use but no documented case reports in literature.

It would be interesting to compare pharmacokinetics and interaction of Sitaglitpin and Vildagliptin with members of DPP enzymes family. In a non-inferiority study comparing Sitagliptin with Vildagliptin suggested comparable clinical efficacy in HbA1c reduction with use of both these agents. They studied nature, type, duration and kinetics of Sitagliptin binding with DPP IV in addition to glucose lowering effects. Both Sitagliptin and Vildagliptin exhibited rapid and effective DPP IV inhibition at 10 mg/kg dose. Sitaglitpin managed to inhibit 90% of DPP IV activity at 60 minutes and >70% inhibition at 8 hours. In comparison a short acting DPP IV inhibitor achieved 80% inhibition at 60 minutes dropping down to 50% at 2 hours. Vildagliptin results were comparable to Sitagliptin as it inhibited >70% DPP IV activity at 8 hours. Sitagliptin is a tight but reversible binder of DPP IV enzyme. Preformed Sitagliptin and DPP IV complex was diluted 100fold excess of substrate and enzyme activity was monitored to assess reversibility. There was a fast recovery of enzyme activity and inhibition was reversed suggesting reversible nature of Sitagliptin binding. The enzyme activity recovery was very slow in case of Vildaglitpin suggesting stronger binding of the later to DPP IV enzyme. Authors also noticed that in fact, Sitagliptin behaved as a pure competitive type of inhibitor as its IC50 values on human plasma DPP-IV increased linearly with substrate concentrations and was highly selective over a variety of proline-specific proteases including DPP8, DPP89, and DPP II in their observation. During the same study Sitagliptin was found to be a rapidly biding agent and rapidly inhibiting DPP IV activity in vivo. In a separate study Vildagliptin has been found to be a slow binding agent although, its dissociation is also slow compared to Sitagliptin as mentioned above [4]. Administration of Sitagliptin and Vildagliptin at 10 mg/kg (p.o.) for 0, 4, 8, and 12 h followed by the oral glucose tolerance test (OGTT) showed glucose lowering of ~ 35% at 8 h [5].

There is no confirmed explanation for thrombocytopenia in patients using Vildagliptin. DPP-8 / DPP-9 inhibition seems the most likely explanation however, not every study [2] found the same effect with DPP 8 DPP 9 inhibition.

DPP IV inhibitors, as a group have been associated in reducing platelet function by reducing platelet aggregation. It is believed that platelets are hyperactive in diabetic patients due to

increase atherosclerosis of blood vessels. This increased atherosclerosis results in platelets overactivity which could potentially lead to increased vascular events in diabetic patients. DPP IV inhibitors reduce platelet aggregation and reduce their function. This effect should lead to less thrombotic events. So far, no studies have been able to conclusively establish the potential beneficial effects of this effect on its own independent of the beneficial effects achieved with improved glycemic control. None of these studies have shown a change in platelet count.

We find it important to report this case as the patient under discussion was not only going to undergo an un-necessary bone marrow biopsy but she experienced stress following discovering the possibility of haemato-logical pathology in view of her age and unexplained nature of drop in cell count. The evidence in this case alone is not strong enough to conclusively associate thrombocytopenia with use of Vildagliptin but we suggest physicians should consider Vildagliptin a possible causative agent in patients with unexplained thrombocytopenia.

References

1. Garber AJ (2011) Thrombocytopenia:Incretin Therapy-Present and Future. Rev Diabet Stud. Rev Diabet Stud 8: 307-322.
2. Lankas GR, Leiting B, Roy RS, Eiermann GJ, Beconi MG et al. (2005) Thrombocytopenia: Dipeptidyl peptidase IV inhibition for the treatment of type 2 diabetes: potential importance of selectivity over dipeptidyl peptidases 8 and 9 Diabetes54: 2988-2994.
3. Burkey BF, Hoffmann PK, Hassiepen U, J. Trappe, M. Juedes et al. (2008) Thrombocytopenia: Adverse effects of dipeptidyl peptidases 8 and 9 inhibition in rodents revisited Diabetes, Obesity and Metabolism 10: 1057-1061.
4. Brandt I, Joossens J, Chen X, Maes MB, Scharpé S, et al. (2005) Thrombocytopenia: Inhibition of dipeptidyl-peptidase IV catalyzed peptide truncation by Vildagliptin ((2S)-{[(3-hydroxyadamantan-1-yl) amino]acetyl}-pyrrolidine-2-carbonitrile) Biochemical Pharmacology 70: 134-143.
5. Davis JA, Singh S, Sethi S, Roy S, Mittra S et al. (2010) Thrombocytopenia: Nature of action of Sitagliptin, the dipeptidyl peptidase-IV inhibitor in diabetic animals Indian J Pharmacol 42: 229-233.