Case Report

Acalculous pyelonephritis and cholecystitis occurring simultaneously in a diabetic patient on sitagliptin therapy

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ABSTRACT

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a new class of anti-diabetic drugs. They control both fasting and postprandial hyperglycemia by inhibiting degradation of incretin hormones, such as, glucagon-like peptide-1(GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Sitagliptin is the first DPP-4 inhibitor to be marketed in India. In addition to its glucose lowering effect, it also suppresses immunity resulting in various infections in a diabetes patient. Here, we describe the simultaneous development of two infections (acalculous pyelonephritis and cholecystitis) in a postmenopausal female patient, well-controlled on sitagliptin-based anti-diabetic therapy.

Key words: Dipeptidyl peptidase-4, infection, oral hypoglycemic agents

INTRODUCTION

Dipeptidyl peptidase (DPP) 4 inhibitors form the mainstay of the add-on therapy to conventional oral hypoglycemic agents (OHAs), at present.[1] Currently, the DPP-4 inhibitors available in India are sitagliptin, vildagliptin, saxagliptin, and linagliptin. DPP-4 is present in plasma and inactivates two incretin hormones — glucagon-like peptide-1(GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). The inhibition of these enzyme results in a greater bioavailability of incretin hormones. As a consequence, insulin secretion from the β-cell increases and glucagon secretion from the α-cell decreases, resulting in a better glycemic control in a diabetes patient.[1] However, beyond their glucose lowering potential, these drugs also have an anti-inflammatory effect, which raises the concern of a possible increase in the occurrence of infections.[2] Here, we describe the simultaneous development of two infections (acalculous pyelonephritis and cholecystitis) in a diabetic patient well controlled on DPP 4 inhibitor based.

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CASE REPORT

A 58-year-old postmenopausal female, who was incidentally diagnosed with type 2 diabetes mellitus (DM) six months back, was on a follow-up with us for the management of her condition [Figure 1]. Her initial fasting plasma glucose (FPG)

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was 450 mg% with an HbA_{1c} of 11.6%, for which a basal bolus regimen of insulin was initiated. Two months later, she was shifted to OHAs (metformin-2 g and glimepiride-4 mg) after achieving euglycemia with insulin therapy. However, the glycemic control deteriorated with OHAs over the next one month. Therefore, sitagliptin (100 mg daily) was added to the existing antidiabetic medications. After initiation of sitagliptin, glycemic control was achieved. Her additional medications included telmisartan, amlodipine, atorvastatin, thyroxine, and calcium/vitamin D. She did not have any chronic complications of DM. However, she developed high grade fever with chills and rigors three months after initiation of Sitagliptin. But her glycemic control was good (FPG - 110 mg% and HbA_{1c} - 7.2%). This was associated with lower abdominal pain and decreased urine output. The provisional diagnosis of urinary tract infection (UTI) was confirmed with urine microscopic examination and culture/sensitivity. Urine culture showed growth of *Escherichia coli*, for which she was started on parenteral antibiotics (meropenem and amikacin) and sitagliptin was stopped. On day 2 of hospitalization, she developed severe pain in the right hypochondrium, associated with tenderness. Ultrasonography of the abdomen and pelvis revealed left sided pyelonephritis, with acalculous cholecystitis, for which conservative medical management was done. She improved symptomatically and was discharged on day 11 of hospitalization.

DISCUSSION

DPP 4 is also expressed as CD26 on the membranes of various cells, including leucocytes. This is involved in T-cell activation, signal transduction, and interactions between the antigen presenting cells and CD4+ T cells.[2] Therefore, an inhibitor like sitagliptin exerts anti-inflammatory effects by downregulating various inflammatory mediators, such as, c-Jun N-terminal kinase (JNK)-1, toll-like receptor (TLR)-4, inhibitory κ-B kinase (IKK-ß), tumor necrosis factor (TNF)-α, interleukin (IL)-6, and the C-reactive protein (CRP).

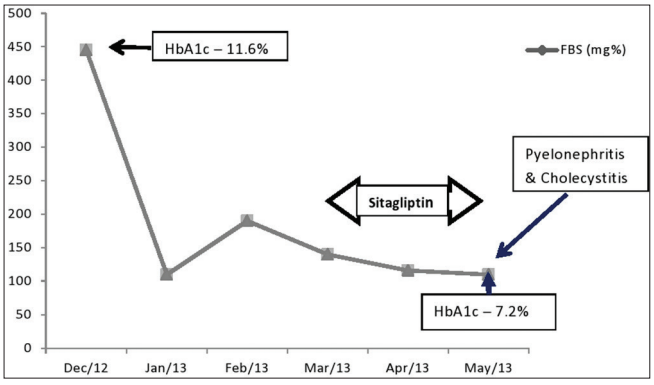

Figure 1: The sequence of events: Sitagliptin therapy, glycemic control, and infections

The immunosuppressive effect of DPP-4 inhibitors has been reconfirmed in various meta-analyses. From the VigiBase (the World Health Organization - Adverse Drug Reactions (WHO-ADR) database), 305,415 suspected ADRs were identified involving antidiabetic drugs in 106,469 case reports, of which 8,083 involved monotherapy with DPP-4 inhibitors. The reporting of overall infections was higher for patients using DPP-4 inhibitors compared to users of biguanides (reporting an odds ratio (ROR) of 2.3 [95% CI 1.9–2.7]). Out of a total of 212 DPP-4–related infections, 24 (11.3%) subjects had multiple infections, similar to our patient. Additionally, the risk of upper respiratory tract infection (URTI) (ROR 12.3 [95% CI 8.6–17.5]) was specifically associated with the use of DPP-4 inhibitors.[3] URTI included acute rhinitis, sinusitis, pharyngitis, and tracheobronchitis in that report. Similarly, a meta-analysis involving 29 studies related to incretin therapy reported that DPP-4 inhibitors had both an increased risk of nasopharyngitis (risk ratio, 1.2 [95% CI, 1.0–1.4] and urinary tract infection (UTI) (risk ratio, 1.5 [95% CI, 1.0–2.2].[4] UTI included cystitis and pyelonephritis. Out of 29 studies, 20 were related to the use of DPP-4 inhibitors (sitagliptin and vildagliptin). A majority of the trials had a duration of less than 30 weeks. Although the increased risk for UTI was associated with both DPP 4 inhibitors equally, the risk for nasopharyngitis was more evident for sitagliptin. However, there was no increased risk of infection with DPP-4 use in a meta-analysis that involved 19 studies, including 7,136 patients randomized to a DPP-4 inhibitor and 6745 patients randomized to another hypoglycaemic drug.[5] These differences in results may be on account of the various confounding factors, such as, the age of the patients, severity/duration of diabetes, other co-morbidities, concomitant use of immunosuppressant drugs such as steroids, duration/dose of DPP 4 inhibitors, and rate of reporting of adverse effects in different studies.

In the present case, there may be an additional contribution of underlying diabetes for the dual infections. However, the data on the direct relationship between diabetes mellitus and infections are inconclusive.[6-8] The mere presence of DM is not always a risk factor for UTI in a postmenopausal female. A prospective cohort study involving 218 diabetic and 799 non-diabetic postmenopausal subjects showed that increased UTI risk occurred mainly in women taking insulin and/or women with a longer diabetes duration (>10 years) compared to their non-diabetic counterparts.[7] The index patient was diagnosed with DM recently and she had good glycemic control on DPP 4 inhibitor–based OHAs. The current literature review shows that the presence of glycosuria associated with high HbA_{1c} significantly increases the risk of UTI.[8] When she developed both infections, her HbA_{1c} was 7.2%. This indicates that her glycemic control was good during the two to three months preceding the infections. Additional

risk factors for infections, such as, bladder dysfunction on account of autonomic neuropathy, cystocele, and calculi in the urinary tract and gall bladder, were also absent in this case.[8] After considering all the factors discussed herein, sitagliptin was probably responsible for the dual infections in our patient (causality assessment using the Naranjo's adverse drug reaction probability (score = 7) and WHO-UMC causality assessment scale).[9,10]

Hence, clinicians must be vigilant during DPP 4 inhibitor therapy in diabetic patients, with regard to the risk of multiple infections. Post-marketing surveillance for these drug related adverse reactions should be done to ensure its safety among diabetic patients, particularly in a country like India.

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