Sitagliptin-Induced Arthralgias: A Case Report

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Case Presentation

On 14 August 2018, B.F., a 56-year-old woman, reported to the clinic for a pharmacist-led diabetes education session secondary to a visit with her provider on the same day. The patient had been diagnosed with type 2 diabetes on 29 May 2018 after completing routine laboratory testing 5 days earlier and was started on the combination therapy sitagliptin/metformin 50/1,000 mg twice daily. B.F.'s laboratory test values drawn on 24 May 2018 are shown in Table 1, and her medication history through the day of the education session is shown in Table 2. The patient was switched from sitagliptin/metformin to sitagliptin 100 mg once daily on 22 June 2018 because she had symptoms including upset stomach, diarrhea, and indigestion from the metformin component of the combination therapy.

During her 14 August 2018 diabetes education session, B.F. revealed that she had been experiencing some neuropathy in her feet and that she had been checking her glucose regularly in the morning (with levels usually ~200 mg/dL). Her last eye exam had been 2 years prior, and she had not yet had a diabetic foot exam. She then reported that 3 weeks into taking the sitagliptin, she began experiencing bad and worsening joint pain, lightheadedness, and constipation. She reported that it caused her to miss work and that she was just not feeling like herself. She discontinued the sitagliptin on her own on 1 August because of this adverse effect.

During her visit with the physician on 14 August 2018, B.F.'s diabetes medication regimen was changed to dulaglutide 0.75 mg once weekly and empagliflozin 25 mg daily. At her next visit on 19 September 2018, she did not report any further joint pain since discontinuing the sitagliptin. She said she was tolerating her medications well and only reported increased urination and a little nausea. B.F. was given a coupon for dulaglutide to help with affordability. Her next appointment was scheduled for 22 January 2019.

Questions

1. Why and how do dipeptidyl peptidase 4 (DPP-4) inhibitors cause arthralgias?
2. Are patients more likely to experience these arthralgia-related symptoms while on DPP-4 inhibitor therapy alone or when taking a combination therapy that includes a DPP-4 inhibitor component?
3. Is this side effect reversed after discontinuing the drug?
4. Should a patient who is experiencing arthralgias associated with DPP-4 inhibitor use switch to a different class of drugs?

Commentary

Diabetes is a common disease affecting >400 million people worldwide. Initial management of type 2 diabetes generally includes diet and exercise, as well as metformin therapy (1). Common second-line agents traditionally have included sulfonylureas, insulin, and thiazolidinediones. Since 2005, additional novel add-on therapies have been introduced, including glucose-like peptide 1 (GLP-1) receptor agonists, sodium–glucose transporter 2 (SGLT2) inhibitors, and DPP-4 inhibitors.

This case highlights a rare adverse effect seen with the use of the DPP-4 inhibitor sitagliptin. Thirty-three cases of arthralgia with DPP-4 inhibitors were identified in the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System database from 16 October 2006 to 31 December 2013. The highest number was reported with sitagliptin (28), with the others coming from saxagliptin (5), linagliptin (2), alogliptin (1), and vildagliptin (2). Twenty-two of the cases occurred within 1 month of initiating DPP-4 inhibitor therapy, and the remainder occurred 44 days to 1 year after starting a DPP-4 inhibitor. Of the 28 reported cases, 23 had symptom resolution

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TABLE 1 B.F.'s Laboratory Test Values on 24 May 2018

Test	Value
A1C, %	10.9
Fasting blood glucose, mg/dL	301
Total cholesterol, mg/dL	266
HDL cholesterol, mg/dL	45
LDL cholesterol, mg/dL	170
Triglycerides, mg/dL	257
Serum creatinine, mg/dL	0.73
Estimated GFR, mL/min/1.73 m^2	93
Serum potassium, mEq/L	4.6
Blood urea nitrogen, mg/dL	14
Systolic blood pressure, mmHg	136
Diastolic blood pressure, mmHg	84
Alanine aminotransferase, units/L	34
Aspartate aminotransferase, units/L	26

within 1 month of discontinuing the DPP-4 inhibitor. Eight cases involved a positive rechallenge, in which individuals stopped treatment, had resolution of symptoms, restarted treatment with the same medication or a different medication in the same class, and had recurrence of the symptoms. Five of the cases also reported positive laboratory assays for systemic autoimmune disorders, but none of these tests were specific to a disorder that would cause severe joint pain (2,3). Lexicomp lists the adverse effect of severe arthralgia with sitagliptin use as occurring in <1%, as determined through postmarketing surveillance or case reports (4).

B.F. did not have any predisposing factors for weaker joints or joint pain noted in her medical record, and she had not previously reported experiencing any joint pain. The pain began after she started sitagliptin and stopped after the medication was discontinued, suggesting that the cause of her pain was the DPP-4 inhibitor sitagliptin. Although rare, arthralgia can affect a patient's life to a severe extent, and these side effects should be addressed as soon as they are reported.

Although B.F. could have been a candidate for insulin therapy based on the American Diabetes Association's *Standards of Medical Care in Diabetes* and both her A1C and fasting blood glucose values (shown in Table 1), patients are often tried on combinations of noninsulin agents to delay the initiation of insulin therapy (5). This patient was diagnosed only 4 months before her August office visit.

Agents are selected based on many factors, including cardiovascular comorbidities, hypoglycemia risk, impact on weight, risk of side effects, cost, and patient preference. B.F.'s current diabetes regimen, including a GLP-1 receptor agonist and an SGLT2 inhibitor, is consistent with the Standards of Care treatment guidelines (5).

Clinical Pearls

- A clear reason why DPP-4 inhibitors might cause arthralgias in some patients remains unknown.
- There is nothing in the literature regarding whether DPP-4 inhibitors as single-therapy agents cause more or fewer arthralgia-related symptoms compared with combination drugs that include a DPP-4 inhibitor as one component.
- Relief of arthralgia-related symptoms is generally seen after discontinuation of the drug.

TABLE 2 B.F.'s Medication History

Medication	Directions	Comments
Sitagliptin/metformin 50/1,000 mg	Take 1 tablet by mouth twice daily	Prescribed on 29 May 2018; discontinued by provider on 22 June 2018
Sitagliptin 100 mg	Take 1 tablet by mouth daily	Prescribed on 22 June 2018; discontinued by patient on 1 August 2018
Dulaglutide 0.75 mg	Inject under the skin every 7 days	Prescribed on 14 August 2018
Empagliflozin 25 mg	Take 1 tablet by mouth daily in the morning	Prescribed on 14 August 2018
Metoprolol XL 50 mg	Take 1 tablet by mouth daily	Prescribed on 29 May 2018
Rosuvastatin 10 mg	Take 1 tablet by mouth at bedtime	Prescribed on 29 May 2018
Hydrochlorothiazide/lisinopril 25/20 mg	Take 1 tablet by mouth daily	Documented medication as of 22 October 2014 (could have been prescribed earlier)

- There are no articles in the literature stating that patients must be switched to a different drug class after experiencing arthralgia-related symptoms with a DPP-4 inhibitor, although some patients have experienced these symptoms after being switched to other drugs in the DPP-4 inhibitor class. The FDA recommends that providers consider avoiding the entire drug class in these cases.

DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

R.J., I.S., and G.V. researched data and wrote the manuscript. R.J. reviewed and edited the manuscript. R.J. is the guarantor of this work and, as such, had full access to all the data reported and takes responsibility for the integrity of the case presented.

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