Linagliptin-Induced Arthralgia

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Case Presentation

A 71-year-old Caucasian man with a history of type 2 diabetes, stage 3 chronic kidney disease, hypertension, coronary artery disease, and depression presented to his primary care provider (PCP) for routine diabetes follow-up. At the time of his visit, his antidiabetic medication regimen included metformin extended release 500 mg twice daily and glyburide 10 mg daily. His other chronic and stable medications included aspirin 81 mg daily, cholecalciferol 1,000 units daily, fenofibrate 145 mg daily, lisinopril 2.5 mg daily, rosuvastatin 5 mg daily, and trazodone 100 mg as needed. The patient reported that he had started a walking routine and reduced his overall dietary carbohydrate intake since his last visit, resulting in a 10-lb weight loss.

Despite these lifestyle changes, his A1C remained elevated at 8.7%; it had been 8.8% previously. It was determined that additional drug therapy was needed for glycemic management. The patient was receptive to a medication change but refused injectable therapies and was unwilling to self-monitor his glucose levels at home. His PCP decided to add the dipeptidyl peptidase 4 (DPP-4) inhibitor linagliptin 5 mg daily to his current regimen.

Nine days later, the patient presented back to the office complaining of new-onset, full-body debilitating arthralgia and back pain. He had taken linagliptin for 8 days and self-discontinued it 1 day before this appointment. He stated that his symptoms began within 24 hours of linagliptin initiation. Initially, he experienced some general full-body aches and localized lower back pain. Around day 5, his symptoms continued to worsen, limiting his ability to do his daily walking. By day 8, he noted not being able to get out of bed without help from his wife.

No other medications had been initiated or discontinued during this time. The patient denied having any drug-induced arthralgia in the past, including any from rosuvastatin or fenofibrate. Other causes of arthralgia, including acute illness, recent vaccinations, or changes to his physical activity, were ruled out based on the patient's report. This reaction occurred before the coronavirus disease 2019 (COVID-19) pandemic; therefore, COVID-19 infection was not part of the differential diagnosis.

At this visit 1 day after discontinuation, the patient reported that his symptoms had started to improve but were not completely resolved; full resolution took 7 more days. The team ordered a comprehensive metabolic panel, along with antinuclear antibody and rheumatoid factor (RF) tests, to rule out other causes. With the exception of an elevated glucose level (167 mg/dL), all results were unremarkable. On physical exam, the patient was afebrile, and no visible swelling in the joints or cutaneous or ocular manifestations were observed. Radiography tests were therefore deemed unnecessary. Based on the Naranjo Adverse Drug Reaction Probability Scale (1), linagliptin-induced arthralgia was considered "probable." Rechallenge with linagliptin or a different DPP-4 inhibitor was not considered appropriate.

Questions

1. Through what proposed mechanism do DPP-4 inhibitors cause arthralgia?
2. Are patients who experience DPP-4 inhibitor–induced arthralgia at higher risk of developing an autoimmune disease such as rheumatoid arthritis (RA)?
3. What, if any, characteristics increase a patient's risk of experiencing DPP-4 inhibitor–induced arthralgia?
4. Is it appropriate to rechallenge with a different DPP-4 inhibitor if a patient experienced arthralgia with a DPP-4 inhibitor?

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Commentary

DPP-4 is a widely expressed serine protease that is found on a variety of cell surfaces, including muscle and immune cells; it deactivates various bioactive peptides (2,3). In the management of type 2 diabetes, DPP-4 inhibition prevents the breakdown of the endogenous incretin hormones glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide. Enhanced expression of these hormones helps to promote glucose-dependent insulin secretion and suppress glucagon in the postprandial state.

Four DPP-4 inhibitors are currently available in the United States: sitagliptin, saxagliptin, linagliptin, and alogliptin. These drugs are most commonly used as an adjunct to metformin when glycemic targets are not met and the need to minimize hypoglycemia and/or weight gain is crucial (4).

Independent of its effects on incretin hormones, DPP-4 enzyme inhibition has been recently linked to immune-related side effects, including joint pain. In 2015, the U.S. Food and Drug Administration (FDA) issued a notice to health care providers and patients warning that DPP-4 inhibitor use has been associated with the development of severe and/or debilitating arthralgia (5). This warning was based on findings from 33 case reports that were submitted between 2006 and 2013 via the FDA's Adverse Events Reporting System database. Each case involved use of one or more DPP-4 inhibitors. Sitagliptin use was linked with the majority of arthralgia cases ($n = 28$), followed by saxagliptin ($n = 5$), linagliptin ($n = 2$), vildagliptin ($n = 2$), and alogliptin ($n = 1$).

An extensive evaluation of such cases has been published and should be reviewed (6). Despite differences in patient presentation, the review highlights three key tenets: *1*) symptoms appeared after the initiation of a DPP-4 inhibitor, *2*) symptoms resolved when the drug was discontinued, and *3*) rechallenge with another DPP-4 inhibitor resulted in subsequent arthralgia in most cases (6). Although most cases of arthralgia occur several weeks to 1 month after DPP-4 initiation, we believe our patient is the first to be documented with a more immediate reaction.

The mechanism of DPP-4 inhibitor–induced arthralgia remains elusive, but several theories have been proposed. Most notably, inhibition of DPP-4 is believed to promote cytokine-induced inflammation in the synovium. Stromal cell–derived factor-1α (SDF-1α), a proinflammatory mediator that is secreted by RA synovial fibroblasts (RASFs), has a specific X-Ala/X-Pro sequence at its N-terminus, making it, and other substrates sharing this sequence, susceptible to degradation by DPP-4 (2). In murine models, DPP-4 inhibition enhances migration of RASFs into the articular space, increasing concentrations of SDF-1α along with other inflammatory mediators such as matrix metalloprotinease (MMP)-1 and MMP-3 (7).

The link between DPP-4 inhibition and symptoms of arthralgia has been established beyond case reports. Researchers of a population-based cohort study examined insurance claims data in Taiwan to determine whether users of DPP-4 inhibitors experienced more frequent severe joint pain (SJP) compared with nonusers (8). After a maximum follow-up of 5 years, use of DPP-4 inhibitors in patients with type 2 diabetes was not associated with an increased risk in SJP or nonspecific arthropathies (8). The authors acknowledged that misclassifications in *International Classification of Diseases*, 9th revision, coding may have influenced their findings.

A meta-analysis of 67 randomized control trials found that DPP-4 inhibitor use is associated with a slight but statistically significant increased risk in overall, but not serious, arthralgia (relative risk 1.13, 95% CI 1.04–1.22, $P = 0.003$) (9). However, the analyzed studies did not provide any insight into the timing of such symptoms, nor did they discuss whether any patients were rechallenged or de-challenged when symptoms occurred.

Most recently, findings from a large retrospective cohort of older adult veterans with diabetes suggest that having a prescription for a DPP-4 inhibitor is associated with increased risk of joint pain (adjusted odds ratio 1.17, 95% CI 1.10–1.24) compared with not having a prescription for a DPP-4 inhibitor (10). Notably, DPP-4 inhibitor users were more likely to have more severe diabetes-related complications, and 50% had an A1C >8%.

Despite the potential for arthralgia, there is a paucity of data supporting DPP-4 inhibitors inducing autoimmunity. A recent study of DPP-4 inhibitor users and nonusers with type 2 diabetes concluded that, although DPP-4 inhibitor use is associated with a more than three times increased risk of arthralgia, autoimmune markers such as RFs and C-reactive protein did not differ between groups (11). The authors comment that these symptoms may be the result of a "change at a

molecular level" and may "not reflect a real autoinflammatory process" (11).

Similarly, a population-based cohort study of >144,000 patients with type 2 diabetes evaluated the incidence of new-onset RA among users of various antidiabetic drugs, excluding insulin (12). After adjusting for risk factors, particularly those associated with RA, the authors found that the use of DPP-4 inhibitors was not associated with an increased risk of developing RA when compared with other antidiabetic drugs (hazard ratio [HR] 1.0, 95% CI 0.8–1.3) (12). The authors further conclude that neither the use of any one specific DPP-4 inhibitor nor the duration of drug exposure affected these findings.

Interestingly, findings from another population-based cohort of ~236,000 patients with type 2 diabetes concluded that metformin plus a newly initiated DPP-4 inhibitor decreases the risk of developing RA and other autoimmune diseases compared with metformin plus another oral antidiabetic medication (HR 0.66, 95% CI 0.44–0.99) (13). These findings further highlight the wide-ranging immune modulatory effects of DPP-4 inhibitors at various receptors throughout the body.

Predicting who will experience arthralgia pursuant to DPP-4 initiation is an impossible task for clinicians. Yet, some evidence indicates that certain characteristics may increase a person's risk. A subgroup analysis of the aforementioned meta-analysis showed that combined use of a DPP-4 inhibitor and other antidiabetic drugs, along with diabetes duration >5 years, enhance this risk (9). Such factors may imply more advanced diabetes. It is therefore hard to discern whether the drug itself or the systemic inflammation caused by insulin resistance and obesity in people with type 2 diabetes is driving the increase in arthralgia risk. According to some data, arthralgia symptoms may be highest within the first year (5,14). Findings from another study suggest that female sex may also contribute (11), but sex and patient age were not thought to contribute to arthralgia risk in other studies (8), so further research is needed.

To date, rates of DPP-4 inhibitor–induced arthralgia in patients with type 2 diabetes and comorbid RA have not been published. Nevertheless, greater monitoring efforts are needed to ensure the safe and effective use of these drugs.

It is important for clinicians to be aware of arthralgia as a potential adverse effect of DPP-4 inhibitors because it is often under-recognized. Because most patients with diabetes should be taking a statin, it is easy to misidentify DPP-4 inhibitor–induced arthralgia for statin-induced myalgia. This error may result in inappropriate discontinuation of the statin without symptom resolution.

Nonetheless, DPP-4 inhibitors remain a core part of the armamentarium for the management of type 2 diabetes. The minimal risk of hypoglycemia, coupled with weight neutrality, make DPP-4 inhibitors good treatment options for select patients.

Clinical Pearls

- Arthralgia is a class effect associated with DPP-4 inhibitors; avoid rechallenge with another DPP-4 inhibitor.
- Health care providers should engage in shared decision-making with patients to ensure that the benefits of DPP-4 inhibitor use outweigh the potential risk of arthralgia.
- Patients starting a DPP-4 inhibitor should be closely monitored for signs and symptoms of joint pain.
- Consider prompt discontinuation of the DPP-4 inhibitor if symptoms are bothersome and/or debilitating. In most cases, symptoms are expected to fully resolve with discontinuation, usually within 1 month (5).
- Arthralgia symptoms may appear in the absence of seropositivity. Ordering of rheumatologic laboratory tests may help differentiate between a true autoimmune disorder and DPP-4 inhibitor–induced arthralgia.

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DUALITY OF INTEREST

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AUTHOR CONTRIBUTIONS

Both authors researched data and wrote and edited the manuscript. Both are guarantors of this work and, as such, take responsibility for the integrity of the article.

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