Injection-Site Nodules Associated With the Use of Exenatide Extended-Release Reported to the U.S. Food and Drug Administration Adverse Event Reporting System

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Glucagon-like peptide-1 (GLP-1) receptor agonists are safe and effective U.S. Food and Drug Administration (FDA)-approved drug products for use in the treatment of type 2 diabetes. To date, the FDA has approved five GLP-1 receptor agonist parenteral formulations: exenatide, liraglutide, exenatide extended-release, and, most recently, albiglutide and dulaglutide. All of these formulations are administered subcutaneously. Exenatide and liraglutide are administered twice daily and once daily, respectively. Until recent approvals of albiglutide and dulaglutide, exenatide extended-release was the only formulation approved for once-weekly use. Relative to other antidiabetic pharmacotherapies, such as metformin or sulfonylureas, GLP-1 receptor agonists are not widely used drugs. A recent study of the usage patterns of antidiabetic drugs estimate that, of 16,316,580 patients prescribed a noninsulin antidiabetic drug in 2012, GLP-1 receptor agonists were dispensed to 673,367 (4.1%) (1).

Exenatide extended-release is formulated to encapsulate exenatide in poly-(D,L-lactide-co-glycolide) (also known as PLG matrix) microspheres, which release the active drug over a sustained time interval (2). PLG is a biodegradable and biocompatible medical polymer with an established safety profile used as a controlled release excipient in a variety of drug products (3). PLG undergoes hydrolysis into lactic and glycolic acids, which are eventually eliminated as carbon dioxide and water. In 2012, the introduction of exenatide extended-release into the U.S. market offered GLP-1 receptor agonist users the advantage of fewer injections per week.

At the time of approval, the FDA was aware of small, largely asymptomatic injection-site nodules that were associated with exenatide extended-release use. Based on the microsphere excipient, injection-site nodules could be expected with exenatide extended-release administration. However, these reactions were considered nonserious and believed to resolve quickly. Based on controlled data provided in the U.S. approved prescribing information, injection-site reactions were observed more frequently in exenatide extended-release users (17.1%) than in those using exenatide (12.7%) or insulin glargine (1.8%). Patient withdrawal because of injection-site nodules was also higher in exenatide extended-release users (0.5%) relative to users of exenatide (0%) or other comparators (0%) (4).

We recently became aware of two publications (5,6) that reported granulomas at the injection sites of exenatide extended-release users. Subsequent to these publications, we reviewed exenatide extended-release–associated injection-site reactions reported to the FDA via the FDA Adverse Event Reporting System (FAERS). The objective of our work was to review and characterize spontaneous (MedWatch)

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TABLE 1. Reports of Exenatide Extended-Release–Associated Injection-Site Nodules Retrieved From FAERS

Case	Age in Years (Sex)	Number of Nodules	Size of Largest Nodule (inches)	Clinical Description	Reported Medical Interventions	Outcome*
2012 Reports Received by FDA						
1	56 (M)	1	2.5	Hard lump, bleeding, pruritic nodule with pain	NR	NR
2	56 (M)	2	2 or 3	Nodule and edema at injection site	H, DC	Recovered
3	62 (M)	4	2.5	Indurated nodule at injection site, redness that transitioned to chest pain and dyspnea	ED, RX, DC	NR
4	42 (F)	Multiple	2	Painful, pruritic granuloma/nodule with warmth at injection site and rash	RX, DC	Not recovered
5	58 (F)	6	<1	Bleeding nodule at injection site	S	NR
6	NR (M)	4	2.5	Erythematous nodules with hives and blisters	ED, RX, DC	NR
7	92 (F)	5	1.2	Hardened nodules at each injection site with swelling, pain, and erythema	DC	Not recovered
8	51 (F)	3	1	Painful, red, pruritic nodules that are warm to touch	NR	Not recovered
9	73 (M)	6	1	Warm and pruritic nodules with burning sensation	DC	Not recovered
10	61 (F)	2	1	Hardened, discolored, swollen, painful nodules with cellulitis	ABX, DC, WC	Recovered
11	NR (F)	4	1	Inflammation, hot, reddened, pruritic nodules with necrotizing adipose via pathology report	S, DC	NR
12	NR (F)	3	4	Pruritic and reddened nodules	RX, DC, ED	NR
13	60 (M)	1	3.9	Bleeding, reddened, warm, inflamed, painful nodule and abscess	S, H, ABX, DC	NR
14	47 (F)	Multiple	2	Large lumps (nodules)	DC	Partial recovery
15	67 (F)	4	2	Discolored, hard nodules in fatty tissue with soreness at injection sites	S	Not recovered
16	68 (M)	Multiple	NR	Small painful nodules with generalized exanthema and pruritis	H, DC	Recovered
17	63 (M)	Multiple	3	Nodule and abscess with redness, pain, and swelling	DC, ABX	Not recovered
2013 Reports Received by FDA						
18	51 (M)	NR	4	Hardened and red nodule with cellulitis	DC, ABX	Recovered
19	53 (F)	Multiple	2	Hardened, pruritic, and red nodules with one site that developed a necrotic abscess	WC	Partial recovery
20	NR (F)	1	1	Swollen, reddened, pruritic nodule with abscess with permanent "knot" at injection site	DC	Partial recovery

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TABLE 1. Reports of Exenatide Extended-Release–Associated Injection-Site Nodules Retrieved From FAERS, *continued from p. 284*

Case	Age in Years (Sex)	Number of Nodules	Size of Largest Nodule (inches)	Clinical Description	Reported Medical Interventions	Outcome*
21	33 (F)	1	1	Large, painful, reddened area with pruritis and warmth	ED, ABX, DC	Not recovered
22	62 (F)	20	1	Nodules described as burning sensation, with bruising, pruritis, and discoloration	DC	Not recovered
23	52 (M)	3	4.25	Nodule and abscess with redness, swelling, pruritis, and pain. Abscess culture fluid (+) for *Staphylococcal aureous*	DC, ABX	Recovered
24	54 (F)	Multiple	1.5	Nodules with swelling, pain, redness, warmth with abscess requiring incision and drainage	H, S, ABX	Partial recovery
25	52 (F)	3	2	Reddened nodules with inflammation and pruritis	DC	Recovered
26	65 (F)	1	1	Reddened nodule with rash, warm to touch, that developed into cellulitis	H, ABX, DC	Partial recovery
27	45 (M)	Multiple	1	Reddened nodules with swelling, pruritis, and hives	BI, ED, RX, DC	Partial recovery

** Outcomes are based on the data provided in the FAERS case at the time of reporting, with "recovered" defined as resolution of nodule, "partial recovery" defined as improvement in nodule size but not complete resolution, and "not recovered" defined as no improvement in the nodule size at the time of reporting.*

ABX, antibiotic administration; DC, discontinuation of exenatide extended-release; ED, treatment in an emergency department or urgent care facility; F, female; H, hospitalization; M, male; multiple, a report that defined the number of nodules as more than one but did specify the exact number; NR, not reported; RX, treatment with corticosteroids (topical, systemic, or direct injection into nodule) or antihistamines (histamine-2 or histamine-1 receptor antagonists); S, surgical intervention; WC, wound care, hot compresses.

reports of exenatide extended-release injection-site nodules submitted to the FDA.

Design and Methods

FAERS Search

We searched the FAERS database for reports of injection-site nodules associated with exenatide extended-release. FAERS has been described elsewhere in detail (7). Briefly, it is a voluntary reporting system comprised of >8 million post-marketing adverse event reports submitted by manufacturers, who have variable reporting requirements to the FDA, and the public. Our search retrieved reports that were coded with a Medical Dictionary for Regulatory Activities preferred term subsumed within the high-level term "injection-site reactions." We date-restricted our search from the FDA date of approval of exenatide extended-release (27 January 2012) through 31 December 2013.

Any FAERS report that met our case definition was included in this case series. Cases must have met one of the following criteria: *1*) contain evidence of an injection-site nodule ≥1 inch in width (with or without abscess) that emerged at an injection site after one or more injections of exenatide extended-release, or *2*) the patient was hospitalized, required a surgical procedure, or required other significant nonsurgical medical intervention to mitigate an injection-site reaction. We defined any other significant nonsurgical medical intervention as requiring treatment by an emergency department or urgent care facility for the reactions, injection of the nodules with steroids or other agents with the goal of reducing the nodule size, or topical or systemic treatment with antibiotics or corticosteroids.

Where available, we extracted information from FAERS reports such as the patient's age, sex, number of nodules or abscesses attributed to exenatide extended-release, number of injections leading up to the event, approximate size of the largest nod-

ule, biopsy or pathology data, clinical description of the reaction, medical interventions required to mitigate the reaction, prior use of exenatide, concomitant use of injectable agents, and outcome. Where appropriate, we summarized these data using proportions and measures of central tendency.

Literature Search

On 29 April 2014, we searched Embase for additional case reports published in the literature but not submitted to FAERS. We selected Emtree-indexed terms in combination to identify reports, using two search strategies. Our searches employed the following terms in combination: *1*) exendin 4 and injection site reaction and *2*) exendin 4 and injection site nodule. We retrieved and reviewed all English-language case reports that further characterized injection-site events among exenatide extended-release users.

Results

FAERS

We retrieved 27 FAERS reports that met our case definition. These cases are summarized in Table 1. The median age of a case was 56 years (range 33–92), and 59% (16/27) of the reports were in females. The majority of cases (78%; 21/27) reported an indication for exenatide extended-release and, among these, 21 reported use of exenatide extended-release in the treatment of type 2 diabetes. Most (81%; 22/27) of these cases were based in the United States.

Reporters described these injection-site reactions as causing local skin discoloration (70%; 19/27), pain or discomfort (56%; 15/27), pruritus (48%; 13/27), warmth (33%; 9/27), and swelling (30%; 8/27) at the injection sites. All cases reported one or more nodules that were characterized as hard, subcutaneous, lumps, masses, or indurations. A minority (22%; 6/27) of cases reported an abscess concurrent with a nodule. Evidence of nodule or abscess biopsy was provided in two reports; only one included a summary of the pathology results, which characterized the lesion as necrotizing adipose tissue. Ten reports provided an estimate for onset latency; among these, 70% (7/10) occurred after the first injection, two occurred after the third injection, and one occurred after the second injection. The number of nodules per patient varied substantially, which suggests that nodules persisted in some patients. The median nodule size was ~2 inches in diameter and ranged from <1 inch to 4.25 inches.

Eight case reports included the need for surgical intervention ($n = 3$), hospitalization ($n = 3$), or both ($n = 2$) to treat the reactions. More than half of the reports (52%; 14/27) documented the need for an emergency department or urgent care visit or use of medications (antibiotics, antihistamines, or corticosteroids). The most commonly reported (78%; 21/27) intervention was to discontinue use of exenatide extended-release. Three cases indicated concomitant use of injectable drugs, all of which reported use of insulin analogs; one patient used liraglutide. Four reports document prior use of immediate-release exenatide without emergence of injection-site reactions such as the nodule formation described here. At the time of report submission, 44% of patients (12/27) reported a partial or full recovery from the injection-site reaction, whereas 30% (8/27) had not reported any improvement in their nodules. Among those cases who reported improvement, we were unable to estimate the time required to recover because of missing data in the reports.

Literature Search

The literature search yielded two case reports of suspected exenatide extended-release–induced injection-site granuloma. We summarize these cases below.

Shan and Guo (5) reported a 62-year-old man who presented to his dermatologist with a skin nodule on his left arm for 5 months. The patient had a medical history significant for type 2 diabetes (diagnosed 5 years earlier), for which he had been receiving daily exenatide injections with no recorded adverse events. Exenatide extended-release had replaced the daily injection regimen, and the patient was receiving the new regimen on his left arm. Approximately 5 months after initiation of the exenatide extended-release injections, a 2-cm subcutaneous nodule without pruritus or tenderness was noted at the injection site. No history of trauma, insect bite, or other cutaneous and systemic disease was noted by the patient. A punch biopsy of the nodule, a technique used to obtain a diagnostic full-thickness skin specimen, was performed, revealing an infiltrate consisting of lymphocytes, histiocytes, eosinophils, neutrophils, and some slight fat necrosis. No microorganisms were identified. The infiltrate was also noted to be present in the dermis at the site of the injection penetration. A diagnosis of sclerosing lipogranulomas was made. The injection site was moved from his left arm to a new and undisclosed location, and he began using rotating sites. The nodule cleared 2 weeks after the new injection practices were initiated without new incident lesions.

Boysen and Stone (6) described a 59-year-old male with type 2 diabetes who presented to the emergency room with a 1-month history of slowly enlarging abdominal nodules. The 1-cm, skin-colored nodules were in the lower abdominal area, and no overlying epidermal changes or erythema was noted on physical exam. The patient was referred to a surgeon, who excised one of the nodules. The excisional biopsy revealed fat necrosis with granulomatous inflammation involving numerous eosinophils and scattered foreign body–type giant cells. No polarizable foreign material was identified, but a further review of the patient's history revealed that the patient had been prescribed exenatide, with which he had been

injecting himself weekly for 6 weeks, with discontinuation of the exenatide therapy 1 month before his presentation. Although the authors did not indicate that the patient was receiving exenatide extended-release, he self-administered "exenatide" once per week, which is the standard dosing regimen for exentatide extended-release.

Discussion

Based on preapproval studies summarized in the prescribing information, the incidence of injection-site reactions attributed to exenatide extended-release is higher than that for immediate-release exenatide (17.1 vs. 12.7%). Data available at approval further suggest that these reactions could result in the formation of small nodules that are benign and self-resolving. However, our assessment of spontaneous reports and published cases demonstrates that exenatide extended-release–associated injection-site reactions may induce large nodule formation and, in isolated cases, may require hospitalization, surgical excision, or some other medical intervention to mitigate. Although the cases described in these reports were not followed longitudinally, at the time of reporting, many cases reported nodules that did not resolve after discontinuing exenatide extended-release, underscoring the importance of educating patients about this risk before prescribing and dispensing. Moreover, the presence of multiple subcutaneous nodules in some cases suggests that nodules are slow to resolve or, in select cases, may be intractable.

The specific mechanism by which exenatide extended-release can cause serious injection-site nodules has not been completely elucidated. Shan and Guo (5) reported a case of nodule formation with histopathologic features consistent with eosinophilic sclerosing lipogranuloma, which these authors speculated may result from a lack of enzyme required to metabolize the long-acting matrix of the dosage form. Boysen and Stone (6) reported the occurrence of enlarging abdominal nodules associated with exenatide extended-release use with surgical excision of the nodules. The specimen contained fat necrosis and chronic granulomatous inflammation with numerous eosinophils and scattered foreign body–type cells. Additionally, one FAERS case reported necrotizing adipose tissue from nodules that were surgically removed. Among our FAERS cases, three reports documented prior use of exenatide immediate-release without nodule formation, but describe subsequent use of exenatide extended-release with nodule development. These cases may support a role of an excipient in these reactions. Based on data we have reviewed, it is not clear that these nodules form from nonhydrolyzed exenatide exended-release excipient attributed to an enzyme defect. Because the clinical description of these cases is consistent with a hypersensitivity reaction (e.g., local induration, warmth, and pruritus), and pathology data consistently reveal the presence of eosinophils and granuloma in these sites, hypersensitivity to the formulation may also be a plausible mechanism.

This case series is based on spontaneous reports identified from FAERS, and inference from these reports has limitations that are important to understand. Adverse events are largely believed to be underreported for FDA-approved products (8), and the rate of reporting is affected by how widely known an adverse event is (e.g., notoriety bias), how long the drug has been marketed, and drug utilization patterns after approval, among other factors. Because of this underreporting, FAERS data cannot be used to estimate the incidence of injection-site reactions for exenatide extended-release users. Additionally, the variable quality of reporting and data omission can make these spontaneous reports difficult to interpret. To partially accommodate for this limitation, we applied a case definition to FAERS reports to ensure the inclusion of minimum data elements for each case. Finally, the submission of a FAERS report does not guarantee that a drug mentioned in the report caused an adverse reaction. However, in this analysis, we are reasonably assured that these reactions are causal because the reactions emerged at the site of injection shortly after injection, and these patients were rarely reported to be using other injectable agents. Where other injectable agents were concomitantly used, all but one were insulin analogs, which are not typically associated with the type of injection-site nodules that we observed in this case series.

We also reviewed FAERS for comparable cases of injection-site reactions with exenatide immediate-release. Although we identified localized and nonserious injection reactions associated with the immediate-release formulation, we did not see reports of large nodules or indurations attributed to the formulation over 9 years of marketing. This is in contrast to the 27 reports for exenatide extended-release over the first 2 years of marketing that we describe here. These data further suggest that excipient in the long-acting dosage form was a likely cause for the reported injection-site nodules.

Health care professionals who care for patients with diabetes who use exenatide extended-release should be aware of the possibility that serious injection-site nodules may occur and, in isolated cases, may require surgical intervention or hospitalization or cause patients to seek additional treatment from emergency or urgent care facilities. Patients should understand this potential risk so that each can make an informed decision with their health care professional when choosing a GLP-1 receptor agonist therapy for the treatment of type 2 diabetes.

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Duality of Interest

The authors are salaried employees of the U.S. government; no potential conflicts of interest were reported.

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