INTRODUCTION

The somatostatin receptor ligands (SRLs), octreotide (SandostatinLAR®), and lanreotide (Somatuline®), are approved by the U.S. Food and Drug Administration (FDA) for the treatment of acromegaly and certain neuroendocrine tumors. These peptide agents may be given parenterally through intramuscular or deep subcutaneous injections and their administration is associated with significant injection-site adverse drug reactions (ADRs).

The reported incidence and nature of these ADRs vary considerably, with the product labeling citing injection-site pain and other injection-site reactions.1 A recent acromegaly patient survey reports injection-site pain in 70% of patients, and nodules, swelling, and bruising in 38%, 28%, and 14% of patients, respectively. 2

OBJECTIVE

The purpose of this study was to compare the incidence and nature of SRL-associated injection-site ADRs reported in the published literature, the product labeling of currently available SRLs, and the FDA-Adverse Events Reporting System (AERS) database.

METHODS

To assess the incidence and nature of SRL-associated injection-site ADRs reported in the literature, a PubMed search was conducted using the following criteria:

- Time period: 1995-2013
- Types of articles: clinical studies, reviews, case reports, position papers
- Search terms: “octreotide”, “lanreotide” (Somatuline®), “somatostatin analogs”, “ADRs of interest: injection-site reaction, skin reaction, granuloma, nodules, lipomatous"

The most current product labeling for the available immediate-release and long-acting octreotide and lanreotide forms was examined for reported incidence of injection-site ADRs.

The FDAAERS quarterly files available to the public from Q1 2004 to Q1 2014 were reviewed. The AERS database contains information on adverse events and medication error reports submitted to the FDA by healthcare professionals, consumers, and other stakeholders. Adverse events reported in patients treated with SRLs were extracted from the AERS database as of 2013.

RESULTS

Injection-Site Reactions Reported in the Literature

- Based on the search criteria, 21 articles were reviewed, including larger comparative studies and case reports. Injection-site pain was reported in up to 76% of patients treated with long-acting octreotide, and nodules were reported in up to 67% of patients receiving octreotide or lanreotide injections. Other injection-site reactions reported in case studies include ulcer, fat necrosis, granuloma formation, and lipomatous reactions.

- Anevoupolous and colleagues (2004) examined the efficacy and tolerability of Somatuline Autogel therapy in 25 acromegaly patients previously treated with Sandostatin LAR. Mild to moderate pain at the injection site was reported by 76% of the patients for Sandostatin LAR and 12% of patients treated with Somatuline Autogel.

- Salvatore and colleagues (2010) looked at injection site reactions in 33 patients treated with Sandostatin LAR who switched to Somatuline Autogel. 59.4% of patients on Sandostatin LAR reported that the injections are somewhat painful as 43.8% of patients on Somatuline Autogel. Moderately painful injections were reported in 8.3% of patients in both groups and very painful injections were reported in 9.4% of patients on Sandostatin LAR only.

- Data from the SCDA study (Salvato et al. 2013) show that 11% (19/166) of patients treated with Somatuline found injections to be extremely painful, 55% (90/166) described them as mild/moderately painful and only 33% (54/166) reported injections to be painless.

- Surprisingly, the majority of patients in the SCDA study on Somatuline still preferred to be injected by a trained nurse as self injection by a family member – only 16% of the patients self-injected while 36% of patients received injections from healthcare professionals.

- Large fat and skin necrosis, injection site granulomas, nodules or lipomatous are reported in various case reports (RiedeJ & Graham 2005; RiedeJ et al. 2010; Bosdoo et al. 2008; Atmaca & Erbas 2005).

- Adelman and colleagues (2012) have shown that Sandostatin LAR had a long acting time (5.3 minutes) with a 2.5% clogging rate. 17Schweinberg and colleagues (2011) described a similar experience with Sandostatin LAR. Anevoupolous and colleagues (2004) noted that the preparation and administration of Sandostatin LAR is a complicated procedure involving multiple steps.

Injection-Site Reactions Reported in Product Labeling

- In the product labeling for long-acting octreotide, injection-site pain is reported in 2%, 9%, and 11% of acromegaly patients receiving doses of 10 mg, 20 mg, and 30 mg, respectively. Among carcinoid patients, injection-site pain was reported in approximately 20% to 40% of patients receiving 10 mg dose and in approximately 30% to 50% at the 20 mg and 30 mg doses.

- The labeling for immediate-release octreotide reports a 1% to 2% incidence of hematoma, bruising, and edema, and 7.7% incidence of pain with injection.

- In the product labeling for long-acting lanreotide, incidence of injection-site reactions, including pain, mass, induration, nodules, and pruritus, was 5%.

Injection-Site Reactions Reported in the FDA AERS Database

A total of 641 injection-site ADRs in 541 cases suspected to be related to the administration of SRLs were reported to the FDA from 2004 to Q1 2014. Events reported in the AERS increased annually from 10 in 2004 and peaked to 236 in 2012 (Figure 1). 3

Figure 1. Annual Number of Injection-Site Reactions Reported for Parenteral SRLs in the FDA AERS Database, 2004-2013

- In the AERS database, the most frequent injection-site reactions reported (Table 1) were injection-site pain, followed by injection-site mass, hematoma, reactions (not specified), swelling, induration, discomfort, erythema, nodules, and hematoma. Other events included pruritus, abscess, inflammation, scar, and bruising.

- Potentially nonreversible injection-site ADRs included injection-site fibrosis, discoloration, induration, scar, calcification, and atrophy.

Table 2. Most Frequent Injection-Site Reactions (10 events) Reported for Parenteral SRLs: FDA AERS Database, Q1 2004-Q1 2014

<table>
<thead>
<tr>
<th>Injection-Site Reaction</th>
<th>n</th>
<th>% of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>306</td>
<td>58.7</td>
</tr>
<tr>
<td>Mass</td>
<td>85</td>
<td>16</td>
</tr>
<tr>
<td>Hematoma</td>
<td>74</td>
<td>8.8</td>
</tr>
<tr>
<td>Reactions (not specified)</td>
<td>63</td>
<td>7.5</td>
</tr>
<tr>
<td>Swelling</td>
<td>40</td>
<td>4.8</td>
</tr>
<tr>
<td>Induration</td>
<td>29</td>
<td>5.4</td>
</tr>
<tr>
<td>Discoloration</td>
<td>26</td>
<td>3.3</td>
</tr>
<tr>
<td>Erythema</td>
<td>28</td>
<td>5.3</td>
</tr>
<tr>
<td>Nodules</td>
<td>27</td>
<td>3.2</td>
</tr>
<tr>
<td>Abscess</td>
<td>12</td>
<td>2.2</td>
</tr>
<tr>
<td>Calcification</td>
<td>17</td>
<td>3.2</td>
</tr>
<tr>
<td>Pruritus</td>
<td>16</td>
<td>3.0</td>
</tr>
<tr>
<td>Bruising</td>
<td>10</td>
<td>1.9</td>
</tr>
</tbody>
</table>

- Injection-site ADRs of significant concern included abscess, inflammation, infection, necrosis, cellulitis, phlebitis, and ulcer.

- The absence of a Wiedner effect (i.e., increase in adverse event reporting in the first 2 years after approval followed by a rapid decline due to a reduction in the number of reporting in the clinically mild or trivial reactions) suggests that the reported reactions were clinically significant.

STUDY LIMITATIONS

- The percentage of patients treated with parenteral SRLs who experience injection-site ADRs cannot be inferred from the FDA AERS database, nor can the relative frequency of these reactions in clinical practice.

CONCLUSIONS

- The spectrum of injection-site ADRs in the literature and the FDA AERS database is wider than that reported in the product labeling of commercially available SRLs. Some ADRs reported to the FDA were of significant concern, including injection-site abscess, inflammation, infection, necrosis, cellulitis, and ulcer.

- The range of injection-site ADRs associated with parenteral SRLs and their potential burden underscores the benefit that an oral octreotide formulation may provide for patients.

References


4. Ultrasound CJ. Presented at: ENDO; March 5-8, 2015; Poster THIR-484.


Disclosures

Havivi Kramer M, Patou G, employees of Chiesa, Inc.