Adverse Event Reports Associated with Injection of Restylane for Lip Augmentation

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Outline

1. Methodology
2. Limitations of data analysis
3. Findings
   - Overall data (119 reports)
     - Lips + other sites (22 reports)
     - Lips as single site (15 reports)
3. Conclusions
Methodology

MAUDE Search Criteria:

- Variations of brand names for “Restylane”.
  - Generated 119 reports since first marketed.
  - Sorted the reports indicating injection into the “lips”, “upper/lower lip”, and “vermillion border”.

- 37 reports injection to lips (31%).
  - 15 reports: Lips (single site).
  - 22 reports: Lips (multiple sites).
Limitations of Data Analysis for Lip Augmentation Reports

- Ambiguous terms used to describe the adverse events, i.e. lumps & bumps, lesion, mass, etc.
- Direct association of the adverse events with the injection of the product is not always identified.
- Unknown pre-injection local anesthetic used in some reports.
- Injection of other products; at the same time or in the past.
- Multiple sites of injection besides injection in the lips.
- Relationship between patients' past history of Restylane injections to adverse events cannot always be identified.
Findings: Overall data-All Reports (n=119)

- Reports’ source: 103 manufacturer & 16 voluntary reporters.
- “Type of Events”- after individual report review:
  - No death, 117 Injury, 2 “Other”.
- Age: Range 28-73 yrs. (99 reports), UNK (20 reports)
- Gender: 110 Female, 8 Male & 1 UNK
  *Only 1 male in the lip augmentation group
Overall Data: Table 1 - Number of Reports by the Year Reports received (n=119)

<table>
<thead>
<tr>
<th>Year Report Received</th>
<th>Q-Med's MDRs</th>
<th>Medicis MDRs</th>
<th>Total # of MDRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2004</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>2005</td>
<td>23</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>2006</td>
<td>11</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>2007</td>
<td>23</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>2008</td>
<td>23</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>2009</td>
<td>1</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>2010</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>2011</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>84</strong></td>
<td><strong>33</strong></td>
<td><strong>117</strong></td>
</tr>
</tbody>
</table>

*2 reports were missing MFR’s name
Overall Data: Figure 1. Top 10 Adverse Events (n=119)

Types of Adverse Events

- Swelling: 44 reports
- Skin Discoloration: 30 reports
- Erythema: 29 reports
- Pain: 23 reports
- Bruise: 16 reports
- Rash: 9 reports
- Burning sensation: 7 reports
- Infection: 6 reports
- Hypersensitivity: 5 reports
- Scarring/Necrosis: 4 reports
Table 2: Number of Reports by the Reported Sites of Injections in the Lip Augmentation Reports (n= 37)

<table>
<thead>
<tr>
<th>Sites of Injections</th>
<th># of MDRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lips. lower lip, upper lip, vermillion border</td>
<td>15</td>
</tr>
<tr>
<td>Lips, upper or lower lip and nasolabial fold</td>
<td>7</td>
</tr>
<tr>
<td>Lips and other unknown sites of the face</td>
<td>7</td>
</tr>
<tr>
<td>Vermillion border and nasolabial fold</td>
<td>4</td>
</tr>
<tr>
<td>Vermillion border, nasolabial fold &amp; lower or upper lip</td>
<td>2</td>
</tr>
<tr>
<td>Vermillion border, nasolabial fold, lips &amp; smoker line</td>
<td>1</td>
</tr>
<tr>
<td>Vermillion border and Botox</td>
<td>1</td>
</tr>
</tbody>
</table>
List of Adverse Events: Reports of Lips & Other Sites of Injection (n= 22)

- Swelling ......................................................... 9
- Skin discoloration ............................................. 5
- Bruise ............................................................. 4
- Allergic reaction/hypersensitivity & anaphylactic shock ....... 4
- Vascular accidents and necrosis ......................... 4
- Hyperpigmentation ............................................. 4
- Erythema .......................................................... 3
Cont’d: Adverse Events in the Lips & Other Sites’ Reports (n= 22)

- Lumps & bumps..............................3
- Herpes break out (+ 1 possible)........3
- Broken capillaries........................2
- Infection.....................................1
- Angioedema.................................1
- Delayed hypersensitivity...............1
- Desquamation, peeling..................1
- Numbness....................................1
- Hypertrophic scar tissue...............1
<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Immediate (first 24 hrs.)</th>
<th>Delayed (after 24 Hrs.)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swelling</td>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Lumps &amp; bumps</td>
<td>0</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Skin discoloration</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Erythema</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>
Table 3 Cont’d. Adverse Events in Lips; Single Site Injections (n=15)

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Immediate (first 24 hrs.)</th>
<th>Delayed (after 24 Hrs.)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angioedema, severe</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Infection &amp; Abscess</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Vas. accident &amp; necrosis</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Broken capillary &amp; granulomas</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Desquamation</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Treatment of Adverse Events

- **Treatment with medication**
  - Steroids: Topical, oral, & intra-lesion injections
  - Oral & IV antibiotics
  - Antihistamines

- **Surgical treatment**
  - Combination therapy
  - I & D of abscess
  - Excision of lesion & biopsy

- **Hospitalization & ER admission**
Conclusion

- **Adverse events not reported in clinical study:**
  - Severe allergic reaction, hypersensitivity, and anaphylaxis
  - Severe swelling
  - Skin discoloration
  - Infection and abscess
  - Vascular accident, necrosis & scarring
  - Severe angioedema

- **Off label use of the device**
  - Product was used in sites other than indicated such as molar region, glabella, lips & marionette line
Conclusion; cont’d

- True incident of adverse events in US cannot be identified due to small number of reports, and low quality of reports.
  - Voluntary reporting of adverse events to FDA such as filling out a MedWatch form by the health care professionals becomes crucial in having a stronger set of data.

- Should FDA decide to approve this product for lip augmentation, the presented MDRs’ data here hopefully will assist the panel members to:
  - Determine the premarket assessment of approvability, and
  - The appropriateness of the post approval studies.