Drug-induced pyoderma gangrenosum (PG), notably with TNF-α inhibitors (TNF-αIs), has been described, but the association has not been well-delineated. The aim of this study is to determine if an association exists between TNF-αI exposure and subsequent PG diagnosis. Using RADAR methodology, the FDA Adverse Event Reporting System (FAERS) was searched for terms related to PG combined with any FDA approved TNF-αI and Proportional Reporting Ratio (PRR) for detection of a safety signal was calculated. The Northwestern Medicine Enterprise Data Warehouse (NMEDW) repository (January 2004 through June 2014 was also (January 2001-July 2017). Data for TNF-αI-exposed patients vs non-exposed were detected. The outcome of interest was a subsequent diagnosis for PG (ICD 9 code: 686.01; ICD-10: L88). Crude and adjusted ORs were calculated by logistic regression analyses. A safety signal was detected in FAERS (N=184, PRR: 5.33; CI: 4.44-6.39) and a significant association between PG and TNF-αI was found in the NMEDW database, (adjusted OR: 9.10, CI: 4.83-17.14, p<0.0001). TNF-αI-exposure showed a significant association with subsequent PG in two large databases. Further exploration of this association for such an important, and often debilitating disorder, is warranted.

Introduction

PG is a rare, ulcerating inflammatory skin disease commonly associated with autoimmune diseases. Drug-induced PG is an even more uncommon entity and can be viewed as a unique subset of PG.1 TNF-αI-induced PG has been described but the association has not been well-established. Moreover, PG is not described as an adverse event in the Full Prescribing Information for any of the TNF-αIs. The aim of this study is to determine if an association exists between TNF-αI exposure and subsequent PG diagnosis within two large databases: FAERS and NMEDW (a large, single-center, urban U.S. patient population, electronic medical record for >5 million patients).

Materials & Methods

Using RADAR methodology,2 the FAERS database (January 2004 through June 2014) was searched for terms related to PG combined with a TNF-αI [certolizumab pegol, infliximab, adalimumab, golimumab, or etanercept], and calculated the Proportional Reporting Ratio (PRR)3 for detection of a safety signal, defined as >3 events, \( \chi^2 > 2 \), and PRR> 2. We queried the NMEDW4 to detect data for all patients with dermatology clinic encounters (Jan 2001 - Jul 2017). Data for all TNF-αI-exposed patients who had a subsequent diagnosis for PG (ICD 9 code: 686.01; ICD-10: L88) were analyzed.

A control population consisted of all patients within the same dermatology population with no exposure to a TNF-αI. Crude and adjusted (for age, gender, and race) OR was calculated using logistic regression analyses.

Results

- A safety signal for PG with all TNF-αIs, as a drug class was detected in FAERS (N=184; PRR: 5.33; CI: 4.44-6.39).
- A significant association between PG and TNF-alpha exposure was detected in NMEDW (table 1), (adjusted OR 9.10, CI 4.83-17.14, p<0.0001).

Table 1: Exposed and non-exposed population in NMEDW

<table>
<thead>
<tr>
<th>TNF-αI exposure</th>
<th>PG</th>
<th>No PG</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>1,872</td>
<td></td>
</tr>
<tr>
<td>No TNF-αI exposure</td>
<td>85</td>
<td>126,479</td>
</tr>
</tbody>
</table>

Discussion

Drug-induced PG is a rare entity and can be viewed as a subset of PG. To our knowledge, this is the first study to demonstrate the significant association of PG secondary to TNF-αI exposure in two large electronic databases.

Given that TNF-αIs are used to treat PG, our findings support the need to determine causality by applying the Naranjo ADR probability scale.

Conclusions

From the FAERS and NMEDW databases, we determined that a significant association exists between TNF-αI exposure and PG. The paradoxical effect of TNF-αI-induced PG is a phenomenon that dermatologists and rheumatologists should be aware of, especially when initiating TNF-αIs on biologic-naive patients.

References