Risk of Pneumocystosis among Patients Receiving Immunosuppressive Therapies: a population based analysis in the United States

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Disclosures

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Pneumocystis Jirovecchi Pneumonia (PJP)

- Opportunistic fungal infection associated with immunosuppressive states
- Up to 40% mortality
- Prophylaxis
  - 1st line: Trimethoprim/Sulfamethoxazole (TSX) thrice weekly
  - 2nd line: Atovaquone, Dapsone, Pyrimethamine, Pentamidine (aerosolized)

Thomas et al. Treatment and Prevention of Pneumocystis Pneumonia in HIV-uninfected patients. UpToDate 2017
Benefits of prophylaxis in Cancer population

- Incidence of PJP is 6.2% among pts with:
  - Leukemias
  - Solid organ transplants
  - Hematopoietic stem cell transplants (HSCT)

- Prophylaxis decreases PJP incidence by 85%:
  - RCT or quasi RCT evidence

- Prophylaxis decreases PJP mortality by 83%:
  - Low quality of evidence

Green et al. Mayo clin proc. 2007;82(9):1052
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Setting</th>
<th>Population</th>
<th># Patients</th>
<th># Cases</th>
<th>PJP Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leshem et al. JAAD 2014;71:284</td>
<td>Single Center</td>
<td>Pemphigus disorders</td>
<td>172</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Amber et al. JAMA Derm 2017;153:1137</td>
<td>Multi Center</td>
<td>Immunobullous</td>
<td>801</td>
<td>1</td>
<td>0.1%</td>
</tr>
<tr>
<td>Lehman et al. JAAD 2010;63:815</td>
<td>Single Center</td>
<td>Psoriasis, SLE, DM, Others</td>
<td>198</td>
<td>1</td>
<td>0.5%</td>
</tr>
<tr>
<td>Li et al. Int J Derm 2011;50:1144</td>
<td>Single Center</td>
<td>Immunobullous</td>
<td>202</td>
<td>4</td>
<td>1.9%</td>
</tr>
<tr>
<td>Gerhart et al. JAAD 2010;62:957</td>
<td>Single Center</td>
<td>CTD and Immunobullous</td>
<td>334</td>
<td>7</td>
<td>2.1%</td>
</tr>
<tr>
<td>Vananuvat et al. Sem Arthritis Rheum 2011;41:497</td>
<td>Single Center</td>
<td>CTD (90% w/ SLE)</td>
<td>138</td>
<td>6</td>
<td>4.3%</td>
</tr>
<tr>
<td>Stern et al. Cochrane Database Syst Rev 2014;10</td>
<td>Multi Center</td>
<td>Leukemia, Solid Organ Transplant, HSCT</td>
<td>1000</td>
<td>62</td>
<td>6.2%</td>
</tr>
<tr>
<td>Green et al. Mayo Clin Proc 2007;82:1052</td>
<td>Multi Center</td>
<td>HSCT, solid organ transplant, hematologic malignancies</td>
<td>414</td>
<td>31</td>
<td>7.5%</td>
</tr>
</tbody>
</table>
Risk/Benefit Profiles

Risks to prophylaxis

- Hyperkalemia
- Agranulocytosis
- Aplastic anemia
- Hemolytic anemia
- Immune thrombocytopenia

- Hepatotoxicity
- Anaphylaxis
- Interstitial nephritis
- SJS/TEN (TSX related incidence $\leq 0.0026\%$)

- 13.8% pts w/o HIV discontinued TSX for any adverse event
- 3.1% pts discontinued TSX due to serious adverse event

Green et al. Mayo clin proc. 2007;82(9):1052
Chan et al. Arch derm. 1990;126(1):43
Study Objective

- To determine overall and age-specific incidence of pneumocystosis in a population without HIV or Cancer that is exposed to corticosteroid and/or immunosuppressive therapies.
Methods: database and population

• Multi-institutional data analytics and research platform (Explorys, IBM Watson Health)

• Clinical data are standardized and curated using Unified Medical Language System (UMLS), a single set of common controlled vocabularies and classifications systems

• Demographically heterogeneous sample
  • Over 56 million unique lives (~ 17% of population)
Methods - Inclusion/Exclusion Criteria

Inclusion
• Active status in the database over 5 year period (2012-2017)
• Age over 18 years

Exclusion
• Diagnosis of HIV or AIDS
• Diagnosis of Malignancy
• Diagnosis of PJP prior to index date
• Diagnosis of PJP prior to exposure
Methods – case cohort and exposures

PJP cases were identified using the SNOMED-CT term “Pneumocystosis”, which has a 1:1 correspondence with ICD-9 code 136.3.

Using the RxNorm ontology for generic and branded drugs, we identified the 4 cohorts with the following exposures:

- **Corticosteroid (CS)**
  - Prednisone
  - Methylprednisolone
  - Prednisolone
  - Dexamethasone

- **Immunosuppressant (IS)**
  - Azathioprine
  - Cyclophosphamide
  - Cyclosporine
  - Methotrexate
  - Mycophenolate mofetil
  - Rituximab
  - Tacrolimus
### Methods – exposure groups

<table>
<thead>
<tr>
<th>Group</th>
<th>CS Prescription</th>
<th>IS prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>Group II</td>
<td>-</td>
<td>✓</td>
</tr>
<tr>
<td>Group III</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Group IV</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Methods – statistical analysis

• The primary outcome of interest was new diagnosis of PJP over the 5 year study period
• Age-specific and overall incidence were calculated for each exposure group
• Incidence stratified by age was compared across treatment groups using the Cochran-Mantel-Haenszel method
• Crude and age-adjusted relative risks and risk differences were estimated with 95% confidence intervals
Patient Demographics

Patient Age Distribution According to Medication Group

<table>
<thead>
<tr>
<th>Group</th>
<th>Age 18-44</th>
<th>Age 45-64</th>
<th>Age 65+</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS alone (N=3,241,500)</td>
<td>41%</td>
<td>37%</td>
<td>23%</td>
</tr>
<tr>
<td>IS alone (N=49,376)</td>
<td>24%</td>
<td>39%</td>
<td>37%</td>
</tr>
<tr>
<td>CS + IS (N=75,210)</td>
<td>23%</td>
<td>43%</td>
<td>35%</td>
</tr>
<tr>
<td>Neither CS nor IS (N=22,736,940)</td>
<td>45%</td>
<td>32%</td>
<td>22%</td>
</tr>
</tbody>
</table>
Results

• We identified 406 new cases of PJP over the 5-year period.
• The overall incidence of PJP in the non-HIV and non-Cancer population was 0.012% (406/3,366,086).

<table>
<thead>
<tr>
<th>Group</th>
<th>PJP Incidence (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS + IS</td>
<td>0.199% (0.187%-0.234%)</td>
</tr>
<tr>
<td>IS alone</td>
<td>0.012% (0.01%-0.017%)</td>
</tr>
<tr>
<td>CS alone</td>
<td>0.008% (0.002%-0.018%)</td>
</tr>
<tr>
<td>Neither</td>
<td>0.001% (0.0004%-0.003%)</td>
</tr>
</tbody>
</table>
Age-specific incidence of PJP by treatment group

Risk of PJP greatest among CS + IS patients
Overall incidence is low

- CS alone (N=3,241,500)
- IS alone (N=49,376)
- CS + IS (N=75,210)
- Neither CS nor IS (N=22,736,940)

* Total number of PJP cases

Age-adjusted risk difference of PJP

Comparison Groups*

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Risk Difference**, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS alone</td>
<td>Neither CS nor IS</td>
<td>0.0064 (0.0054 - 0.0074)</td>
</tr>
<tr>
<td>IS alone</td>
<td>Neither CS nor IS</td>
<td>0.0105 (0.0008 - 0.0202)</td>
</tr>
<tr>
<td>CS + IS</td>
<td>Neither CS nor IS</td>
<td></td>
</tr>
<tr>
<td>CS+ IS</td>
<td>IS alone</td>
<td>0.1978 (0.1659 - 0.2297)</td>
</tr>
</tbody>
</table>

* CS - Corticosteroid; IS - Immunosuppressant
** Risk difference is defined as the incidence of PJP infection in group 1 minus the incidence of PJP infection in group 2. Risk differences were adjusted for age using the Cochran-Mantel-Haenszel method.
Discussion

• Overall incidence of PJP among patients exposed to IS, CS, or a combination is very low (0.012%)

• Patients across all age groups receiving both CS and IS therapy appear to be at highest risk (PJP incidence range: 0.19%-0.23%)
  – Incidence of PJP, as well as the relative risk, are greatest among patients exposed to combination IS and CS
Discussion

• TSX prophylaxis is recommended in non-HIV/AIDS and non-Cancer patients receiving both CS and IS.
  – Incidence of SJS/TEN in patients receiving TSX prophylaxis ≤ 0.03%
  – Risk of PJP in this subgroup is 6.33-7.67 times higher than the risk of SJS/TEN

• TSX prophylaxis may be associated with severe AE requiring withdrawal in 3.1%
  – Risk of severe AE requiring withdrawal is 13.5-16.3 times higher that the risk of PJP in this subgroup
  – Alternative forms of prophylaxis in patients who do not tolerate TSX may also be considered
Strengths

• Largest and most heterogeneous cohort of patients exposed to IS and/or CS
  – Overcome selection biases and limitations inherent to small cohorts recruited within specialty centers
  – Generalizable

• Included patients with all types of baseline disease
  – While baseline disease status and immunologic aberrancy is likely to contribute to risk of PJP, exposure to iatrogenic IS, especially in combination, may be the stronger driver of PJP risk
Limitations

• Use of administrative data for case identification may result in misclassification bias

• We could not confirm concomitant use of CS and IS

• We could not assess dose and duration of exposures

• Low number of events associated with some medications did not allow for stratification of risk by medication
Conclusions

• Very low overall risk of PJP among patients without HIV/AIDS or cancer who are exposed to iatrogenic immunosuppression

• PJP incidence highest among patients on combination IS and CS

• The decision to initiate prophylaxis should be based on a balanced consideration of risks and benefits
  – PJP prophylaxis for patients receiving combination IS and CS therapy may be warranted
Thank You

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