Tumor Necrosis Factor-α Inhibitor (TNFi) utilization among women with live birth pregnancies

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Disclosures

• Co-authors are employees of the US Food and Drug Administration and Harvard Pilgrim Health Care Institute

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Background

• Epidemiological data suggest chronic inflammatory conditions affect women of child-bearing age
  - Incidence of Inflammatory Bowel Disease* is highest among 20-40 year olds
  - Rheumatoid Arthritis occurs later in life but affects women predominantly
  - Psoriatic Arthritis and Psoriasis affect men and women equally, presents primarily in 30-50 year olds
  - Ankylosing Spondylitis occurs more in men and peaks between ages 20 and 40 years old

• Tumor Necrosis Factor-α inhibitors (TNFis), important therapy for managing chronic inflammatory conditions (after/concurrent with corticosteroids, methotrexate)

• Data on the use and safety of TNFis during pregnancy is limited

*Inflammatory Bowel Disease (UC: ulcerative colitis; CD: Crohn’s Disease)
Objective

To characterize TNFi use during pregnancy among women with a chronic inflammatory condition who delivered a live born infant by examining:

– What is the pattern of TNFi use among women with at least 1 chronic inflammatory condition (CID) who delivered a live born infant?

– Does the pattern of TNFi use during pregnancy differ from use among non-pregnant women of the same age with CID?
Methods:
Data & Pregnancy Cohort Identification

• Data: 01/01/2004 – 09/30/2015 from 16 data partners participating in Sentinel

• Pregnancy Cohort Eligibility Criteria:
  – Women 15-54 years old who delivered a liveborn infant
  – At least 480 days (approx. 16 months) of medical and drug coverage from delivery admission
  – Presence of at least 1 outpatient ICD-9 code for chronic inflammatory condition diagnosis: RA/JRA, AS, UC, CD, PsO, PsA during baseline period (183 days prior to pregnancy start)

RA: rheumatoid arthritis, JRA: juvenile rheumatoid arthritis,
UC: ulcerative colitis, CD: Crohn’s disease,
AS: ankylosing spondylitis, PsO: Psoriasis, PsA: psoriatic arthritis
Create a Comparator Cohort of Non-pregnant women without Live-Birth

- Women with enrollment requirements relative to live-birth date were identified
  - Same Age and Duration of eligibility criteria
- Matched women without a live-birth episode on age, indication, site and calendar time period

Louisa
Age: 22
Condition: RA

Gretl
Age: 22
Condition: RA
Exposure Episodes

- Using national drug codes (NDC) and procedure codes, identified these TNFis: etanercept, adalimumab, golimumab, certolizumab and infliximab.

- Assigned the number of days on the maintenance dose for each TNFi, accounting for multiple injections per pack.
  - For example, etanercept prescribed weekly, will be assigned 14 days for a two-injection pack.
TNFi Episodes during the study period

-90 days

1st 2nd 3rd

Trimesters of Pregnancy

Query Start

Pregnancy start (index date) OR Non-Pregnancy Start

Query End

TNFi Episodes

TNFi Episodes

Delivery date OR Matched date
Analyses

1. Prevalence of any TNFi use, stratified by inflammatory condition among pregnant and non-pregnant women
2. Prevalence of individual TNFi use, stratified by pregnancy trimester for each condition
3. Prevalence of any TNFi use, stratified by maternal age among pregnant and non-pregnant women
4. TNFi-specific annual prevalence of use from 2004 through 2015 among pregnant and non-pregnant women
RESULTS
### Cohort Characteristics for total cohort and women with pre-existing inflammatory condition, exposed to a TNFi during pregnancy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All pregnancies</th>
<th>RA Pregnancy</th>
<th>JRA Pregnancy</th>
<th>AS Pregnancy</th>
<th>PsO Pregnancy</th>
<th>PsA Pregnancy</th>
<th>CD Pregnancy</th>
<th>UC Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total unique pregnancy episode</td>
<td>2,220,332</td>
<td>4,047</td>
<td>418</td>
<td>354</td>
<td>6,791</td>
<td>633</td>
<td>3,748</td>
<td>3,690</td>
</tr>
<tr>
<td>Maternal age at delivery, years (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-20</td>
<td>5.2</td>
<td>1.2</td>
<td>10.0</td>
<td>0.6</td>
<td>2.0</td>
<td>0.8</td>
<td>2.1</td>
<td>1.5</td>
</tr>
<tr>
<td>20-24</td>
<td>13.0</td>
<td>6.5</td>
<td>16.7</td>
<td>6.2</td>
<td>6.8</td>
<td>4.9</td>
<td>8.9</td>
<td>6.0</td>
</tr>
<tr>
<td>25-29</td>
<td>26.0</td>
<td>22.4</td>
<td>25.6</td>
<td>24.0</td>
<td>22.6</td>
<td>18.3</td>
<td>25.1</td>
<td>24.4</td>
</tr>
<tr>
<td>30-34</td>
<td>33.4</td>
<td>37.1</td>
<td>33.5</td>
<td>35.6</td>
<td>38.9</td>
<td>37.9</td>
<td>39.6</td>
<td>39.8</td>
</tr>
<tr>
<td>35-39</td>
<td>17.9</td>
<td>25.3</td>
<td>11.2</td>
<td>27.1</td>
<td>23.7</td>
<td>29.4</td>
<td>19.8</td>
<td>22.2</td>
</tr>
<tr>
<td>40-44</td>
<td>4.1</td>
<td>6.2</td>
<td>2.9</td>
<td>5.4</td>
<td>5.5</td>
<td>7.9</td>
<td>3.8</td>
<td>5.6</td>
</tr>
<tr>
<td>45-54</td>
<td>0.5</td>
<td>1.4</td>
<td>0.0</td>
<td>1.1</td>
<td>0.5</td>
<td>0.8</td>
<td>0.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Any code for preterm birth (%)</td>
<td>7.4</td>
<td>10.1</td>
<td>9.6</td>
<td>9.6</td>
<td>6.9</td>
<td>11.7</td>
<td>9.8</td>
<td>10.5</td>
</tr>
<tr>
<td>Any code for post-term birth (%)</td>
<td>14.5</td>
<td>10.6</td>
<td>11.5</td>
<td>12.4</td>
<td>14.3</td>
<td>13.3</td>
<td>11.6</td>
<td>11.6</td>
</tr>
</tbody>
</table>

Data source: Sentinel Distributed Database
Data years 2004-2015
Use of any TNF inhibitor in any pregnancy trimester for live birth pregnancies and among matched non-pregnant women (years 2004-2015 combined)

Percent of cohort with any TNFi use

Chronic Inflammatory Condition

- AS
- PsO
- PsA
- JRA
- CD
- RA
- UC

Pregnant
Matched non-pregnant

Percent of TNFi use in non-pregnant population minus Percent of TNFi use in pregnant population
TNF Inhibitor use by trimester, among women with a livebirth, stratified by indication (2004-2015)

**Rheumatoid Arthritis**

- **Pregnancy Trimester**
  - 90 days prior
  - 1st
  - 2nd
  - 3rd
  - Non-pregnant

**Juvenile Rheumatoid Arthritis**

- **Pregnancy Trimester**
  - 90 days prior
  - 1st
  - 2nd
  - 3rd
  - Non-pregnant

**Ankylosing Spondylitis**

- **Pregnancy Trimester**
  - 90 days prior
  - 1st
  - 2nd
  - 3rd
  - Non-pregnant

**Psoriatic Arthritis**

- **Pregnancy Trimester**
  - 90 days prior
  - 1st
  - 2nd
  - 3rd
  - Non-pregnant
TNF Inhibitor use by trimester, among Psoriasis Patients with a livebirth, stratified by indication (2004-2015)

A. Using the same axis scale as in previous slide

B. Increased axis scale to examine trends
TNF Inhibitor use by trimester, among women with a livebirth, stratified by indication (2004-2015)

**Crohn's Disease**

- **90 days prior**: 10% ADA, 5% ETAN, 5% GMB, 2% CERT, 3% IFX
- **1st**: 15% ADA, 10% ETAN, 10% GMB, 5% CERT, 5% IFX
- **2nd**: 20% ADA, 15% ETAN, 15% GMB, 10% CERT, 10% IFX
- **3rd**: 25% ADA, 20% ETAN, 20% GMB, 15% CERT, 15% IFX
- **Non-pregnant**: 30% ADA, 25% ETAN, 25% GMB, 20% CERT, 20% IFX

**Ulcerative Colitis**

- **90 days prior**: 5% ADA, 5% ETAN, 10% GMB, 0% CERT, 15% IFX
- **1st**: 10% ADA, 10% ETAN, 15% GMB, 5% CERT, 20% IFX
- **2nd**: 15% ADA, 15% ETAN, 20% GMB, 10% CERT, 25% IFX
- **3rd**: 20% ADA, 20% ETAN, 25% GMB, 15% CERT, 30% IFX
- **Non-pregnant**: 25% ADA, 25% ETAN, 30% GMB, 20% CERT, 35% IFX

Approved TNFis: ADA, IFX, CERT

Approved TNFis: ADA, IFX, GMB
Use of a specific TNF Inhibitor among pregnancies ending in live births with chronic inflammatory conditions, stratified by age (2004-2015)

Use of a specific TNF Inhibitor among non-pregnant women with chronic inflammatory conditions, stratified by age (2004-2015)

Sample size of pregnant and non-pregnant cohorts showing no differences in underlying disease distribution

<table>
<thead>
<tr>
<th>Cohort</th>
<th>AS</th>
<th>CD</th>
<th>PsA</th>
<th>RA</th>
<th>JRA</th>
<th>PsO</th>
<th>UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant</td>
<td>367</td>
<td>1404</td>
<td>4588</td>
<td>7597</td>
<td>4526</td>
<td>1056</td>
<td>143</td>
</tr>
<tr>
<td>Not pregnant</td>
<td>362</td>
<td>1368</td>
<td>4514</td>
<td>7529</td>
<td>4494</td>
<td>1055</td>
<td>143</td>
</tr>
</tbody>
</table>
Use of a specific TNF Inhibitor among pregnancies ending in live births with chronic inflammatory conditions (2004-2015)

Use of a specific TNF Inhibitor among non-pregnant women with chronic inflammatory conditions (2004-2015)

*Not all data partners contributed to all study years for the trend analysis*
Discussion of Key Findings

• TNFi selection and duration of use during pregnancy is specific to underlying inflammatory condition
  – Strong preference for Etanercept in RA, JRA, PsA, PsO and AS pregnancies despite availability of other approved TNFis
  – Preference for Infliximab in CD and UC pregnancies
  – Decreased use of any TNFi in 2nd and 3rd trimesters in RA, JRA, PsA, PsO and AS pregnancies not observed in IBD pregnancies
    • Patients with IBD are advised to continue medication during pregnancy

• Older pregnant women were more likely treated with TNFis compared to non-pregnant counterparts
  – Possibly due to differences in disease severity during pregnancy
  – Limited therapeutic options for older patients (poor control of blood glucose with corticosteroids)

• Annual trend analyses reflect dynamics between approvals for expanded indications and the decision to treat during pregnancy
Study Strengths

• Size of study cohort; large number of pregnancies suitable to assess a population with identified chronic inflammatory condition

• Age-, calendar year- and disease-matched non-pregnant cohort allows comparison to a reference population

• Use of dispensing data for exposure ascertainment minimizes recall bias
Limitations

• Gestational age is not available in claims data, but derived from a validated algorithm
  – Possible misclassification of pregnancy duration and exposure timing relative to pregnancy timeline
  – Gestational age, estimated from ICD-9 codes from mother’s claims, may have reduced sensitivity
• Comparator cohort may include women who were pregnant and had an outcome other than a liveborn delivery
• Disease severity measure not available in claims data
Thanks to
Data Partners who provided data used in the analysis.
TNF Inhibitor use by trimester, in the cohort women with pre-existing Ulcerative Colitis with a livebirth delivery during 2004-2015