Methotrexate and Tumor Necrosis Factor-α Inhibitor Use is Associated with Decreased Risk of Cardiovascular Disease in Rheumatoid Arthritis Patients

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Introduction
• RA is characterized by chronic systemic inflammation
• Cardiovascular disease (CVD) is the leading cause of death
• MTX and tumor necrosis factor (TNF)-α inhibitors have been associated with ↓ risk of CVD in RA
• Prior studies did not adjust for inflammatory burden or lipid profiles
• Observational data need to be replicated

Objectives
• To examine the relationship between methotrexate and TNF-α inhibitor use and the development of CVD in an RA inception cohort using electronic health records
• We hypothesized that the use of MTX or TNF-α inhibitors is associated with a reduction in risk of incident CVD

Methods – Patients
• Inclusion criteria
  – Incident adult RA patients (ICD-9 code 714.0 at ≥ 2 outpatient encounters with a rheumatologist)
  – Identified through EHR
  – RA diagnosis validated against 1987 ACR criteria by manual review of 100 random charts, with 97% concordance
• Exclusion criteria
  – Prevalent CVD

Methods - Outcome
Incident CVD
• coronary artery disease (CAD)
• cardiac revascularization procedure
• stroke
• abdominal aortic aneurysm
• transient ischemic attack
• peripheral artery disease
• arterial revascularization procedure
Methods - Covariates

Demographics
- Age, gender, ethnicity

Comorbidities
- BMI (kg/m²), SBP/DBP, HTN, hyperlipidemia, diabetes
- ESR, CRP, LDL, RF, anti-CCP antibodies

Laboratory measures
- NSAIDs, glucocorticoids, hydroxychloroquine (HCQ), MTX, TNF-α inhibitors, statins

Medications
- NSAIDs, glucocorticoids, hydroxychloroquine (HCQ), MTX, TNF-α inhibitors, statins

Propensity score (by multivariate regression models)
- For probability of a patient taking MTX or TNF-α inhibitor

Methods - Statistical modeling

- Patients classified as ever or never users of MTX or TNF-α inhibitors (for descriptive statistics only)
- Incidence rates (IR) of CVD calculated using Poisson regression models
- Relative risk (RR) for incident CVD by quartiles of cumulative exposure calculated using Poisson regression models
- Hazard ratio (HR) for incident CVD by median cumulative exposure calculated using time-varying Cox proportional hazard regression models

Results - Study population

RA patients at GHS by EHR
- N=1,871

RA patients without prevalent CVD by EHR
- N= 1,819

RA patients with prevalent CVD by EHR
- N=52*

RA patients without prevalent CVD by chart review
- N=1,718

Patients with prevalent CVD by chart review
- N=111*

Results – Patient characteristics

Included incident RA patients (n = 1,718)
- Follow up (median) 3.4 y
- Female 73%
- Age at RA diagnosis (median) 57 y
- Caucasian 95%
- RF positive 77%
- BMI (median) 29 kg/m²
- NSAIDs (ever) 71%
- Steroids (ever) 84%
- Hydroxychloroquine 38%
- Methotrexate 62%
- TNF-α inhibitors 33%

Results - Outcome

- 127 cases of incident CVD confirmed by chart review
  - 48 CAD
    • Myocardial infarction
    • Unstable angina
    • Cardiac revascularization procedure
  - 45 Stroke/TIA
  - 34 PAD/AAA

CVD incidence by MTX use

<table>
<thead>
<tr>
<th></th>
<th>MTX, non-users n=710</th>
<th>MTX users n=1119</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median exposure</td>
<td>22 months</td>
<td>37</td>
</tr>
<tr>
<td>Incident CVD cases</td>
<td>90</td>
<td>37</td>
</tr>
<tr>
<td>Cases/1000 p-y</td>
<td>23.2 (18.8-28.5)</td>
<td>14.6 (10.6-20.1)</td>
</tr>
<tr>
<td>Incidence rate ratio</td>
<td>0.63 (0.43-0.83)</td>
<td></td>
</tr>
</tbody>
</table>

*Excluded patients (n=163) slightly younger, otherwise no differences
RA: rheumatoid arthritis, GHS: Geisinger Health System
Risk of developing CVD in RA patients by duration of methotrexate use

<table>
<thead>
<tr>
<th>MTX use (quarters)</th>
<th>Never use</th>
<th>≤ 9 months</th>
<th>&gt;9-22 months</th>
<th>&gt;22-40 months</th>
<th>&gt;40 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>652</td>
<td>258</td>
<td>274</td>
<td>268</td>
<td>285</td>
</tr>
<tr>
<td># of CAD</td>
<td>70</td>
<td>19</td>
<td>16</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Adjusted RR (95% CI)</td>
<td>1.41</td>
<td>0.98</td>
<td>0.58</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.350</td>
<td>0.947</td>
<td>0.100</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, race, propensity score, body mass index, history of hypertension, hyperlipidemia and diabetes, ESR, CRP, RF and anti-CCP antibodies, and use of glucocorticoids, HCQ, TNF-α inhibitors, and NSAIDs.

Risk of developing CVD by cumulative MTX use

<table>
<thead>
<tr>
<th>Methotrexate use</th>
<th>Never</th>
<th>≤ 22 months</th>
<th>&gt;22 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>652</td>
<td>532</td>
<td>534</td>
</tr>
<tr>
<td>No. of CVD events</td>
<td>70</td>
<td>35</td>
<td>22</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.15</td>
<td>(0.71-1.86)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

CVD incidence by TNF-α inhibitor use

- Median exposure
  - TNF-α inhibitor non-users: n=1241
  - TNF-α inhibitor users: n=588
- Incident CVD cases
  - 110
- Cases/1000 p-y
  - 20.8 (17.3-25.1)
  - 14.9 (9.2-23.9)
- Incidence rate ratio
  - 0.72 (0.43-1.19)

Risk of developing CVD by duration of TNF-α inhibitors use

<table>
<thead>
<tr>
<th>TNF-α inhibitor use (quarters)</th>
<th>Never use</th>
<th>≤ 8 months</th>
<th>&gt;8-17 months</th>
<th>&gt;17-35 months</th>
<th>&gt;35 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>1147</td>
<td>147</td>
<td>139</td>
<td>144</td>
<td>141</td>
</tr>
<tr>
<td># of CAD</td>
<td>102</td>
<td>12</td>
<td>4</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Adjusted RR (95% CI)</td>
<td>1.59</td>
<td>0.41</td>
<td>0.50</td>
<td>0.07</td>
<td>0.07</td>
</tr>
<tr>
<td>P value</td>
<td>0.004</td>
<td>0.182</td>
<td>0.135</td>
<td>0.010</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for propensity score, age, gender, race, propensity score, body mass index, history of hypertension, hyperlipidemia and diabetes, ESR, CRP, RF and anti-CCP antibodies and use of NSAIDs, glucocorticoids, HCQ and MTX.
### Probability of developing CVD by TNF-α inhibitor use

<table>
<thead>
<tr>
<th>Time (months) since RA diagnosis</th>
<th>Never</th>
<th>≤ 17 months</th>
<th>&gt; 17 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>1147</td>
<td>286</td>
<td>285</td>
</tr>
<tr>
<td>≤ 17 months</td>
<td>777</td>
<td>175</td>
<td>281</td>
</tr>
<tr>
<td>&gt; 17 months</td>
<td>515</td>
<td>77</td>
<td>238</td>
</tr>
</tbody>
</table>

#### Limitations
- Observational - Confounding by indication?
- Outcome broadly defined to include all CVD due to small number of events
- No information on smoking, family history of CVD, level of physical activity and use of ASA
- Homogenous population - applicability to other populations?

### Conclusions
- In this inception RA cohort, use of MTX > 22 months was independently associated with a 72% reduction in risk of incident CVD
- Use of TNF-α inhibitors > 17 months was independently associated with a 69% reduction in risk of incident CVD
- Our findings are biologically plausible, given the role of inflammation in atherosclerosis and the potent anti-inflammatory effects of these medications that may take several months to manifest their effect
- These findings suggest that these medications are protective against CVD in a group of patients at high risk for CVD

### Results – Patient differences
Differences as expected in patient population treated with these medications

- MTX or TNF-α inhibitor users vs. nonusers
  - younger at age of RA dx
  - higher BMI
  - Higher inflammatory markers
  - more anti-CCP pos
  - more nonsteroidal, TNF-α inhibitors or MTX

- MTX users vs. non users
  - More female
  - Less on HCQ

- TNF-α inhibitor users vs. nonusers
  - More NSAIDs

Thank you

Geisinger Medical Center, Danville, PA