Predicting randomized clinical trial results with real-world evidence: A case study in the comparative safety of tofacitinib, adalimumumab and etanercept in patients with rheumatoid arthritis

- Clinical Background, Motivation and my Experience at F2F meeting

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Disclosure

• None.
Rheumatoid Arthritis

• A chronic Inflammatory Condition
  • Joints
  • Extra-articular involvement

• Global prevalence ~ 0.24%\(^1\)

• Co-morbidities and mortality
  • Infection
  • Lymphoproliferative disorders
  • Cardiovascular disorders
  • Increased risk for premature mortality
Pharmacologic Management of RA

• **Disease-Modifying AntiRheumatic Drugs**: DMARDs

  Synthetic DMARDs
    - **PILLS**
    - Conventional Synthetic csDMARDs
    - Targeted Synthetic tsDMARDs
    - Biological originator bDMARDs

  Biological DMARDs
    - **INJECTIONS or INFUSIONS**
    - Biosimilar DMARDs

  EXAMPLES
  - Methotrexate (MTX)
  - Tofacitinib (TOF)
  - Etanercept (ETN)
  - Adalimumab (ADA)
Pharmacologic Management of RA

- MTX
- Short-term glucocorticoid

Inadequate Response (IR)

Stratify based on prognosis

Another csDMARDs or Triple therapy

Add: bDMARDs or tsDMARDs

MTX + ADA or MTX + ETN vs. MTX + TOF

Summarized from Smolen et al. 2018
<table>
<thead>
<tr>
<th>Tofacitinib (TOF)</th>
<th>Adalimumab (ADA)</th>
<th>Etanercept (ETN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Jak Kinase inhibitor</td>
<td>TNF monoclonal Ab</td>
</tr>
<tr>
<td>Dosage/Route</td>
<td>Oral, 5mg twice a day</td>
<td>SubQ inj, 40mg Q2W</td>
</tr>
<tr>
<td>Warnings and Precautions</td>
<td>Serious infections</td>
<td>Serious infections</td>
</tr>
<tr>
<td></td>
<td>Invasive fungal infection</td>
<td>HepB reactivation</td>
</tr>
<tr>
<td></td>
<td>HepB reactivation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymphoma &amp; Malignancy</td>
<td>Lymphoma &amp; malignancy</td>
</tr>
<tr>
<td></td>
<td>Lymphopenia, neutropenia, anemia</td>
<td>Cytopenia,</td>
</tr>
<tr>
<td></td>
<td>Gl perforation</td>
<td>Demyelinating diseases</td>
</tr>
<tr>
<td></td>
<td>Liver enzyme elevation</td>
<td>Heart failure</td>
</tr>
<tr>
<td></td>
<td>Lipid abnormalities</td>
<td>Lupus-like syndrome</td>
</tr>
<tr>
<td>Approved Indications</td>
<td>RA – 11/2012</td>
<td>RA; JIA; PsA; AS; PsO</td>
</tr>
<tr>
<td></td>
<td>PsA – 12/2017</td>
<td>~ 2000</td>
</tr>
</tbody>
</table>

Summarized from Drug Package Inserts.
**Tofacitinib vs. TNFi** -

- **ORAL Strategy trial**: one year, double blinded, non-inferior, head-to-head comparison
  - TOF (n=384) vs.
  - MTX + TOF (n=376) vs.
  - MTX + ADA (n=386)

- **Efficacy**:
  - MTX + TOF was non-inferior to MTX + ADA when assessing ACR50 at 6 months

- **Safety**: at one year:

**Table 3: Summary of adverse events, serious adverse events, and discontinuations in the safety analysis set**

<table>
<thead>
<tr>
<th></th>
<th>Tofacitinib monotherapy (n=384)</th>
<th>Tofacitinib and methotrexate (n=376)</th>
<th>Adalimumab and methotrexate (n=386)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of adverse events*</td>
<td>598</td>
<td>652</td>
<td>620</td>
</tr>
<tr>
<td>Patients with adverse events</td>
<td>226 (59%)</td>
<td>231 (61%)</td>
<td>253 (66%)</td>
</tr>
<tr>
<td>Patients with treatment-related adverse events</td>
<td>101 (26%)</td>
<td>111 (30%)</td>
<td>133 (35%)</td>
</tr>
<tr>
<td>Patients with serious adverse events</td>
<td>35 (9%)</td>
<td>27 (7%)</td>
<td>24 (6%)</td>
</tr>
<tr>
<td>Patients discontinuing due to adverse events</td>
<td>23 (6%)</td>
<td>26 (7%)</td>
<td>37 (10%)</td>
</tr>
<tr>
<td>Patients with severe adverse events (defined by the investigator)</td>
<td>24 (6%)</td>
<td>17 (5%)</td>
<td>23 (6%)</td>
</tr>
<tr>
<td>Deaths†</td>
<td>2 (1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Adverse events of special interest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious infections</td>
<td>6 (2%)</td>
<td>10 (3%)</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Herpes zoster (serious and non-serious)</td>
<td>4 (1%)</td>
<td>8 (2%)</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Herpes zoster (serious and non-serious) in patients who were vaccinated</td>
<td>1/69 (1%)</td>
<td>2/75 (3%)</td>
<td>0/72 (0%)</td>
</tr>
<tr>
<td>Opportunistic infections (excluding tuberculosis)</td>
<td>2 (1%)</td>
<td>1 (&lt;1%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>0</td>
<td>2 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>MACE (non-fatal)</td>
<td>0</td>
<td>0</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Malignancy (excluding non-melanoma skin cancer)</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-melanoma skin cancer</td>
<td>2 (1%)</td>
<td>0</td>
<td>1 (&lt;1%)</td>
</tr>
</tbody>
</table>

*Data are n, n (%), or n/N (%). MACE = major adverse cardiovascular event (includes non-fatal myocardial infarction, fatal cardiovascular event, and non-fatal cerebrovascular accident). †Patients could have had more than one adverse event. ††One patient died of septic shock; one patient died of atypical pneumonitis and respiratory distress syndrome associated with influenza A.

1. Fleischmann et al. 2017
Tofacitinib vs. TNFi -

• Observational study\textsuperscript{1}:
  • MarketScan database (2011-2014)
  • RA patients, previously treated with MTX, newly start on
    • DMARDs (n=5399) vs.
    • TNFi +/- DMARDs (n=13367) vs.
    • Non-TNFi Biologics +/- DMARDs (n=2902) vs.
    • TOF +/- DMARDs (n=164)
  • Effectiveness – assessed by a claim-based algorithm
  • Safety – Occurrence of serious infections requiring hospitalization

\textsuperscript{1} Machado et al. 2018
An ongoing Phase 3b/4 study

- Safety Study Of Tofacitinib Versus Tumor Necrosis Factor (TNF) Inhibitor In Subjects With Rheumatoid Arthritis (NCT02092467)
- 5-year, open label, randomized study
- Intervention: TOF 5mg BID vs. TOF 10mg BID vs. ADA or ETN
- Study Subjects:
  - I/C:
    - Age > 50 yo
    - moderate to severe RA
    - IR to MTX
    - One CV risk factor
  - E/C:
    - Current or recent infection
    - Clinically significant lab abnormalities
    - pregnancy
- Primary Outcomes: malignancy, Incidence of MACE
- Secondary Outcomes: Opportunistic Infections, Hepatic events, CV events other than MACE, all cause mortality, DAS28, ACR20, CDAI, ACR50, ACR70, HAQ-DI
Study objective

• To compare the safety of tofacitinib with adalimumab and etanercept in patients with rheumatoid arthritis in a retrospective, observational, comparative cohort study.

• We will replicate the design and population inclusion criteria of an ongoing phase 3b/4 randomized clinical trial (NCT02092467), with the aim of predicting the RCT results using real-world evidence from OHDSI.
Primary Hypothesis

- No difference in the incidence of malignancies (excluding non-melanoma skin cancer) between tofacitinib and adalimumab in patients with rheumatoid arthritis
- No difference in the incidence of malignancies (excluding non-melanoma skin cancer) between tofacitinib and etanercept in patients with rheumatoid arthritis
- No difference in the incidence of MACE between tofacitinib and adalimumab in patients with rheumatoid arthritis
- No difference in the incidence of MACE between tofacitinib and etanercept in patients with rheumatoid arthritis
Study Design

• Retrospective, observational, comparative cohort Design
  • Target cohort
  • Comparator cohort
Data source

• Multiple data sources across OHDSI community
### Study Population (target and comparator cohorts)

<table>
<thead>
<tr>
<th>CLINICAL TRIAL (NCT02092467)</th>
<th>OBSERVATIONAL STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moderate to severe rheumatoid arthritis</strong></td>
<td>At least one diagnosis of rheumatoid arthritis one or prior to index exposure (moderate-to-severe inferred by initiation of biologic therapy)</td>
</tr>
<tr>
<td><strong>Adults &gt;/= 50 years</strong></td>
<td>Adults &gt;/= 50 years *</td>
</tr>
<tr>
<td><strong>Taking methotrexate without adequate control of symptoms</strong></td>
<td>At least one record of prior exposure to methotrexate *</td>
</tr>
<tr>
<td><strong>Have at least one cardiovascular risk factor</strong></td>
<td>At least one condition record for hypertension, hyperlipidemia, diabetes mellitus, or myocardial infarction prior to index exposure or at least one record suggesting current smoker status *</td>
</tr>
<tr>
<td><strong>No Current or recent infection</strong></td>
<td>At least one condition record of infection on or in prior 30 days from index exposure *</td>
</tr>
<tr>
<td><strong>No Clinically significant laboratory abnormalities</strong></td>
<td>Exactly zero measurement records with numeric value outside normal range on or in 60 days prior to index exposure *</td>
</tr>
<tr>
<td><strong>No Pregnancy</strong></td>
<td>Exactly zero condition, procedure, measurement or observation records indicating pregnancy in 270 days before to 90 days after index exposure *</td>
</tr>
</tbody>
</table>

For the secondary analyses, the criteria marked with a star (*) will be removed one at a time, starting with the last one, to explore the influence of these restrictions on the estimated effect.
Outcomes

• Malignancy, excluding non-melanoma skin cancer
• Incidence of MACE (non-fatal stroke, MI, and cardiovascular death)

• Negative Control outcomes
Covariates

• Demographic
• Conditions/condition aggregation
• Drugs/drug aggregation
• Risk scores, e.g. Charlson comorbidity index
Statistical Analysis

- To compare the target cohort with the comparator cohort for the hazards of outcome during the time-at-risk using Cox proportional hazards model

- Time-to-event: The earliest of
  - 1) the first occurrence of the outcome
  - 2) the end of the time-at-risk window (censored) – on treatment analysis
  - 3) the end of the observation period (censored) – intent to treat analysis

- Propensity score

- Random-effects meta-analytic estimates to pool evidence across the databases for all comparison-outcome-analyses where there was sufficient homogeneity ($I^2 < 40\%$)
During F2F meeting: