Welcome to the OHDSI Face-to-face NYC 2018

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Janssen Research and Development,
Columbia University Medical Center
Why are we here?
Take 10 minutes to complete survey

Look in your email for note from Maura/Kristin or go to:

https://goo.gl/forms/nkYtjBmgWcghUDsH3
The journey to real-world evidence

- Patient-level data in source system/schema
- Reliable evidence

[Diagram showing the journey from patient-level data to reliable evidence]
Different types of observational data:

- **Populations**
  - Pediatric vs. elderly
  - Socioeconomic disparities

- **Care setting**
  - Inpatient vs. outpatient
  - Primary vs. secondary care

- **Data capture process**
  - Administrative claims
  - Electronic health records
  - Clinical registries

- **Health system**
  - Insured vs. uninsured
  - Country policies
The journey to real-world evidence

Types of evidence desired:
- **Cohort identification**
  - Clinical trial feasibility and recruitment
- **Clinical characterization**
  - Treatment utilization
  - Disease natural history
  - Quality improvement
- **Population-level effect estimation**
  - Safety surveillance
  - Comparative effectiveness
- **Patient-level prediction**
  - Precision medicine
  - Disease interception
Agenda

Day 1
• Group: align on shared problem(s)
• Group photos! 10am
• Break out: design and implement the study
• Group: review progress

Day 2
• Group: execute study across data partners
• Group: synthesize results
• Group: Discuss evidence generation process
F2F objectives

1. Answer a clinical question:

“Predicting randomized clinical trial results with real-world evidence: A case study in the comparative safety of tofacitinib, adalimumab and etanercept in patients with rheumatoid arthritis” Lead: Bridget Wang

2. Learn about improving the real-world evidence generation process:

“It takes a village: An open-science approach to improving the quality and efficiency of the real-world evidence generation process” Lead: Kristin Feeney
Comparative safety of tofacitinib, adalimumab and etanercept in patients with rheumatoid arthritis – Clinical Background and Motivation

Runsheng “Bridget” Wang, MD
Division of Rheumatology, CUMC
Department of Biomedical Informatics, Columbia University
Rheumatoid Arthritis

- A **chronic** inflammatory condition, primarily involving joints.
  - Inflammation in synovium -> pain and swelling of joint
  - Uncontrolled inflammation -> damage in cartilage and bone -> joint damage
- Affecting 1.5 million people in the United States
- Clinical presentation:
  - Chronic joint pain, swelling, morning stiffness
  - Symmetrical, small joints > large joints
  - Extra-articular involvement: rheumatoid nodules, myositis, vasculitis, interstitial lung diseases, pericarditis/myocarditis, scleritis/episcleritis, Sjogren’s syndrome, hematologic abnormalities
- Comorbidities and Mortality:
  - Infection
  - Lymphoproliferative disorders
  - Cardiovascular disorders
  - Increased risk for premature mortality
- Diagnosis: Clinical symptoms, blood tests, imaging studies
Management of RA

• Goal of treatment:
  – stop inflammation
  – prevent joint damage
  – improve/reserve physical function
  – reduce long-term complications
Pharmacologic Management of RA

• **Disease-Modifying AntiRheumatic Drugs**: DMARDs
  – conventional synthetic DMARDs (csDMARDs) – first line treatment
    • Methotrexate (MTX), Sulfasalazine (SSZ), Hydroxychloroquine (HCQ), Leflunomide (LEF), etc.
  – biologic DMARDs (bDMARDs) – infusion or injection
    • TNFi: e.g. Adalimumab (ADA), Etanercept (ETN), etc.

• CTLA antagonist: abatacept (ABT)
Pharmacologic Management of RA

• When patient failed first csDMARDs:
  – Treatment decision is based on:
    – Efficacy
      • No significant difference between bDMARDs vs. tsDMARDs $^{1,2,3}$
        – ORAL Strategy trial: TOF vs. TOF + MTX vs. ADA + MTX
    – Safety
      • Short-term safety data: RCTs
      • Long-term safety data: observational studies, e.g. LTE, registries, cohort studies, etc.

1, Chatzidionysiou et al, 2017
2, Nam et al, 2017
3, Fleischmann et al, 2017
<table>
<thead>
<tr>
<th></th>
<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>
<td>TNF receptor antagonist</td>
</tr>
<tr>
<td>Dosage/Route</td>
<td>Oral, 5mg twice a day</td>
<td>SubQ inj, 40mg Q2W</td>
<td>SubQ inj, 50mg QW</td>
</tr>
<tr>
<td>Warnings and Precautions</td>
<td>Serious infections</td>
<td>Serious infections</td>
<td>Serious infections</td>
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<tr>
<td></td>
<td></td>
<td>Invasive fungal infection</td>
<td>Fungal infection</td>
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<tr>
<td></td>
<td></td>
<td>HepB reactivation</td>
<td>HepB reactivation</td>
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<tr>
<td></td>
<td>Lymphoma &amp; Malignancy</td>
<td>Lymphoma &amp; malignancy</td>
<td>Lymphoma &amp; malignancy</td>
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<tr>
<td></td>
<td>GI perferation</td>
<td>Demyelinating diseases</td>
<td>Demyelinating disease</td>
</tr>
<tr>
<td></td>
<td>Lymphopenia, neutropenia, anemia</td>
<td>Cytopenia,</td>
<td>Pancytopenia, aplastic anemia</td>
</tr>
<tr>
<td></td>
<td>Liver enzyme elevation</td>
<td>Heart failure</td>
<td>Heart failure</td>
</tr>
<tr>
<td></td>
<td>Lipid abnormalities</td>
<td>Lupus-like syndrome</td>
<td>Lupus-like syndrome Autoimmune hepatitis</td>
</tr>
</tbody>
</table>
Safety Outcomes

- Infections
  - Serious infections
  - Opportunistic infections: e.g. tuberculosis, herpes zoster
- Malignancies
- Cardiovascular diseases
- Mortalities
- Lab abnormalities: lipid profile, renal function, liver enzymes
- Hematological abnormalities
- GI side effects
- Demyelinating disease
- Induction of autoimmune diseases
- Teratogenicity
Tofacitinib vs. TNFi -

- **ORAL Strategy trial**\(^1\):
  - TOF (n=384) vs.
  - TOF + MTX (n=376) vs.
  - TOF + ADA (n=386)

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

- **Safety:**

<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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse events of special interest</th>
<th>Tofacitinib monotherapy</th>
<th>Tofacitinib and methotrexate</th>
<th>Adalimumab and methotrexate</th>
</tr>
</thead>
<tbody>
<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 event). *Patients could have had more than one adverse event. †One patient died of urosepsis; one patient died of atypical pneumonia and respiratory distress syndrome associated with influenza A.

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

1. Fleischmann et al. 2017
• Observational study\textsuperscript{1}:
  – MarketScan database (2011-2014)
    • 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
    • Overall low
    • TNFi, non-TNFi bio > TOF > DMARDs
  – Safety – Hazards of serious infection were not significantly different

\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)
- 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
- Intervention: TOF 5mg BID vs. TOF 10mg BID vs. ADA or ETN
- 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
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