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

- Clinical Background, Motivation and my Experience at F2F meeting

Runsheng “Bridget” Wang, MD
Division of Rheumatology, Columbia University Medical Center
DBMI, Columbia University

Disclosure

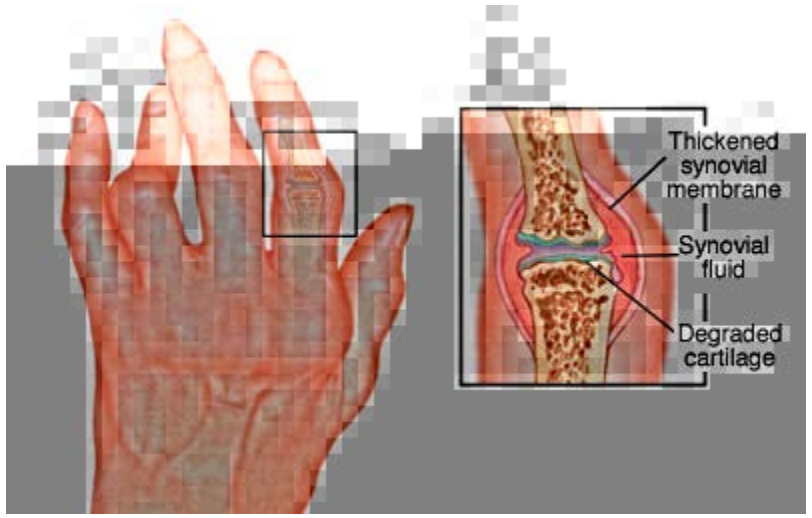
- None.

Rheumatoid Arthritis

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

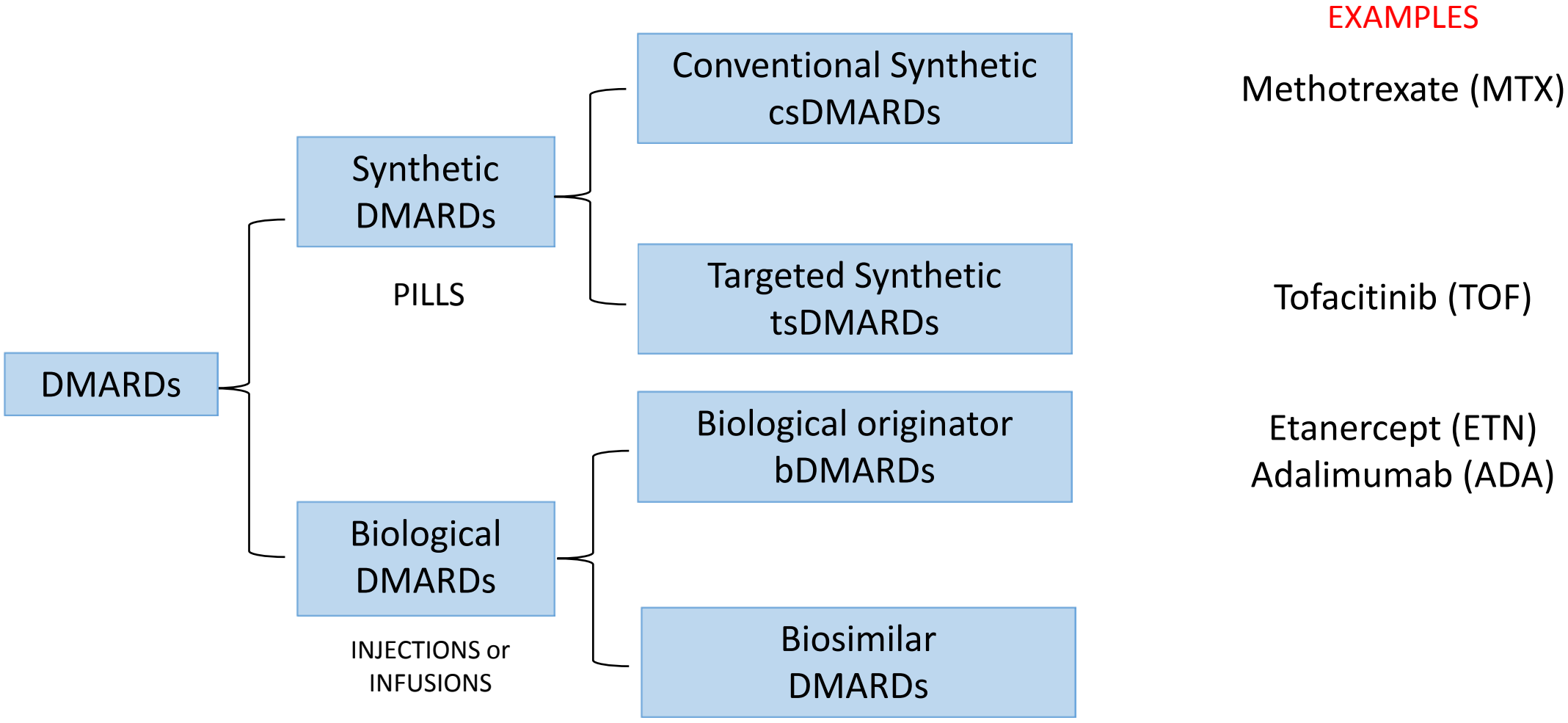
- Global prevalence ~ 0.24%[1]

- Co-morbidities and mortality
  - Infection
  - Lymphoproliferative disorders
  - Cardiovascular disorders
  - Increased risk for premature mortality



Pharmacologic Management of RA

- **D**isease-**M**odifying **A**nti**R**heumatic **D**rugs: DMARDs



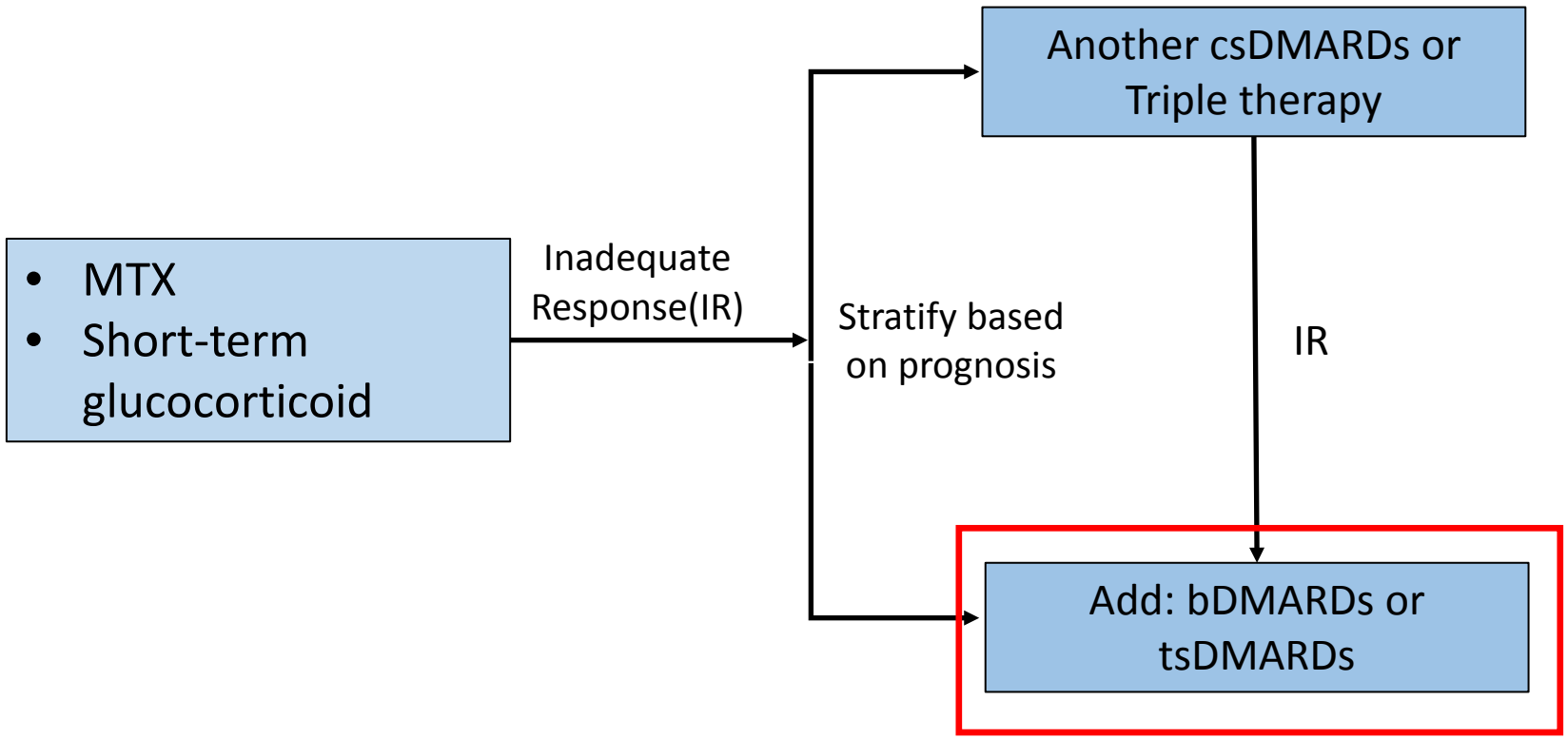
EXAMPLES

Methotrexate (MTX)

Tofacitinib (TOF)

Etanercept (ETN)
Adalimumab (ADA)

Pharmacologic Management of RA



MTX + ADA or MTX + ETN

vs.

MTX + TOF

Summarized from Smolen et al. 2018

	Tofacitinib (TOF)	Adalimumab (ADA)	Etanercept (ETN)
Mechanism	Jak Kinase inhibitor	TNF monoclonoal Ab	TNF receptor antagonist
Dosage/Route	Oral, 5mg twice a day	SubQ inj, 40mg Q2W	SubQ inj, 50mg QW
Warnings and Precautions	Serious infections	Serious infections Invasive fungal infection HepB reactivation	Serious infections Fungal infection HepB reactivation
	Lymphoma & Malignancy	Lymphoma & malignancy	Lymphoma & malignancy
	Lymphopenia, neutropenia, anemia	Cytopenia,	Pancytopenia, aplastic anemia
	GI perforation	Demyelinating diseases	Demyelinating disease
	Liver enzyme elevation	Heart failure	Heart failure
	Lipid abnormalities	Lupus-like syndrome	Lupus-like syndrome Autoimmune hepatitis
Approved Indications	RA – 11/2012 PsA – 12/2017	RA; JIA; PsA; AS; PsO ~ 2000	RA; JIA; PsA; AS; PsO; Crohn's; UC; HS ~2000

Summarized from Drug Package Inserts.

Tofacitinib vs. TNFi -

- ORAL Strategy trial[1]: 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:

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

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 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

Tofacitinib vs. TNFi -

- Observational study[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

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)
- https://clinicaltrials.gov/ct2/show/NCT02092467?cond=NCT02092467&rank=1
- 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)

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

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: