Designing Target Trials Using Electronic Health Records: A Case Study Of Second-line Disease-modifying Anti-rheumatic Drugs And Cardiovascular Disease Outcomes In Patients With Rheumatoid Arthritis

https://doi.org/10.1371/journal.pone.0305467

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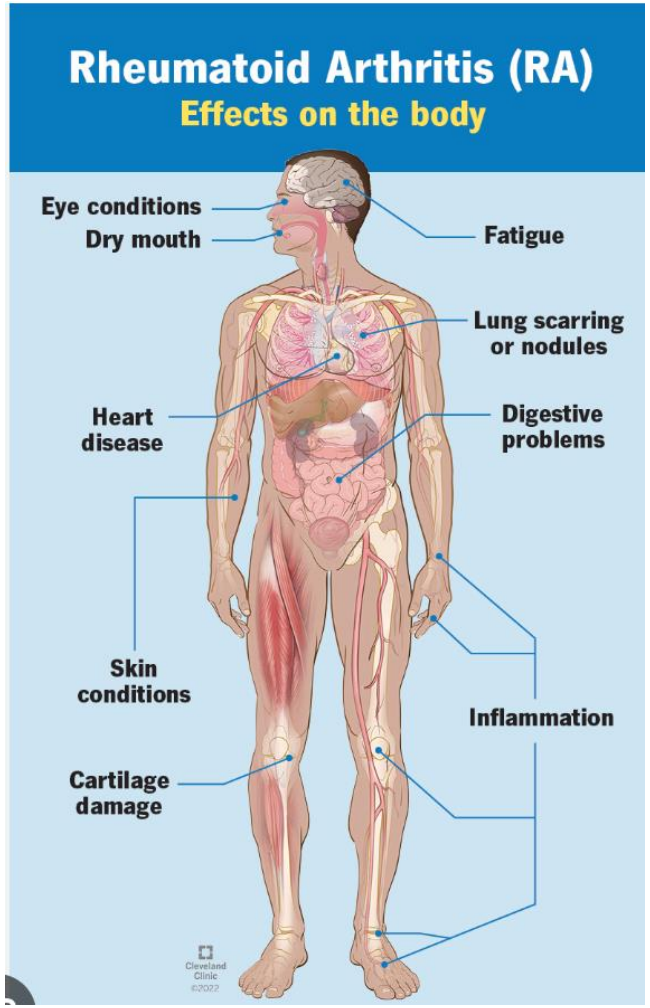
Presenter

Rheumatoid Arthritis (RA)

- RA is a chronic inflammatory disease characterized by broad activation of the innate and adaptive immune systems
- Due to immune activation, people with RA have an increased risk of cardiovascular disease (CVD)
- Treatment includes non-steroidal anti-inflammatory drugs (NSAIDs), steroids and disease-modifying anti-inflammatory drugs (DMARDs)



Introduction

- RCTs are the gold standard in the evidence of comparative effectiveness research(CER), crucial for developing guidelines
- Not feasible or ethical and does not represent the target populations
- Researchers have turned to observation data including EHRs to conduct CER
- Expand generalizability of treatment effects in more diverse populations

Rationale

- Meta-analyses including only RCTs concluded that the addition of DMARDs did not reduce CVD risk in RA patients,
- A meta-analysis that included both RCTs and observational studies suggested that adding DMARDs provided some benefit
- The discrepancy may be attributed to observational studies, such as selection bias, immortal time bias, and unmeasured confounding
- To address issues with observational studies, EHR data from a large regional academic health system to emulate a (hypothetical) open-label pragmatic trial comparing methotrexate (MTX) alone to MTX plus DMARD therapy to assess their effect on CVD risk in RA patients.

Materials and methods

- Specifying the target trial (TT)
  - Design the TT to assess the effect of an intervention on the outcome
  - Collaboration with clinicians or domain experts
  - Considerations
    - Eligibility criteria
    - Treatment strategies
    - Assignment procedures
    - Follow-up period
    - Outcome
    - Causal contrasts of interest
    - Analysis plan

Materials and methods

- Selecting data source
  - Should be of reasonable quality and size
  - Sufficient variation in treatment is available
  - Outcome events are prevalent enough
  - Reliable diagnostics algorithms exist
  - No major changes in data capture occurred
  - Irregular time visits and informed presence bias need to be accounted
  - Created the de-identified and anonymized EHR data from the North-western Medicine Enterprise data warehouse date June 21 to July 16, 2020

Materials and method

- Eligibility criteria
    - Should reflect the populations
    - Eligible to receive either treatment
    - Treatment contradictions should be excluded
    - Demographic exclusions should be reviewed
    - The operational definition should consider available data
    - Ideally, RA diagnoses are confirmed by trained clinicians
    - Not feasible with EHR, ICD codes
    - New cases of RA were taken to capture new second-line treatment users

Materials and methods

- Treatment strategies
  - RCTs have control over mode, dose and timing of interventions
  - EHR has more treatment variation if there are no specific treatment guidelines
  - The definition of the intervention should closely match the actions
  - Compare MTX monotherapy to those who receive additional treatment to DMARD

Materials and methods

- Specifying a grace period
  - RCTs have clear Randomisations points
  - EHRs do not necessarily share the same timing of treatment initiation/discontinuation
  - Comparing never to ever DMARD use without specifying the timing of initiation leads to selection bias
  - The too-strict definition of exactly 8 weeks after MTX use can reduce the sample size
  - Include of grace period: wherein eligible patients have the option of initiating a treatment strategy
  - Captures more individuals and mimics real-world practice
  - Eligibility criteria: a minimum MTX treatment duration– 8 weeks and eligible to initiate DMARD
  - Eligible participants are granted a grace period of 24 months which either initiates DMARD (active treatment) or not (control)

Materials and methods

- Assingment procedures
  - Treatment assignment relies on randomisation in RCTs and gives an unbiased estimation of ITT effects
  - TT should be a pragmatic design
  - Conditional on measured confounders is essential to achieve randomisation from EHR data
  - Several strategies have been used – propensity score matching, stratification, g computation, inverse probability weighting and Doubly robust methods
  - Variables must be properly selected at baseline that can influence the treatment assignment and outcome
  - Timing of confounders definition matters to maintain the temporality

Materials and methods

- Outcomes
  - Follow-up should be long enough to capture outcomes of interest
  - Occurrence of Major Adverse Cardiac Events (MACE)
    - Non-fatal myocardial infarction
    - Non-fatal stroke
    - Incident heart failure
    - Cardiovascular death
  - Identified using ICD-9 and ICD-10 codes
  - Death from all-causes

Materials and methods

- Follow-up period
  - TT framework, “time zero” is the point in time when an individual meets eligibility criteria, treatment is assigned, and follow-up begins
  - It coincides with the date of first treatment received in an RCT
  - The definition of “time zero” varies with a clinical research question
    - Met a single time eg. Remdesivir for COVID-19
    - Multiple time points eg . Hormone therapy for menopausal women
  - The selection of time zero is important to prevent immortal time bias
  - Loss to follow-up in EHR studies needs to include a measure of inactivity or disenrollment in the healthcare system
  - The date of prescription was defined as time zero

Materials and methods

- Causal contrasts of interest
  - Since observational studies do not have randomised treatment, they can only estimate the protocol effect
  - Attempted to estimate the observational analogue of an ITT effect by specifying the protocol

Materials and methods

- Statistical analysis
  - IPTW survival models or baseline-covariate adjusted survival models can be used to estimate ITT effects
  - Per-protocol effects
    - Estimating time-varying inverse probability of adherence weights
    - Estimating IPTWs using a logistic regression model with treatment as outcome and baseline covariates as predictors
    - Using a weighted pooled logistic regression model
    - Resulting model can be used to calculate marginal survival curves risk differences at select times, 5-year mean restricted survival time, and the average hazards ratio over follow-up
    - Covariates can be selected by existing theory and knowledge
  - Non-parametric bootstrapping can be used to calculate (1-α)% confidence intervals

Materials and methods

- Artificial introduction of immortal time bias due to the specification of a treatment grace period
  - Event during the grace period before initiating a DMARD, randomly assign them to treatment strategy. There is no need for the inverse probability of adherence weights
  - Clone all individuals at baseline. Assing clone A to MTX, and clone B to initiate a DMARD within 24 months

Materials and methods

- Missing data
  - Single imputation for missing baseline variables
  - Carried last observations forward for 2 years for time varying covariates

Results

Table 3. Demographic and clinical characteristics of included patients with rheumatoid arthritis at baseline and stratified by treatment strategy after 24 months, northwestern medicine, January 2000–June 2020.

	Baseline	After 24 months	
	Overall (n = 659)	Addition of Second-Line DMARD Therapy during grace period (n = 287)^	MTX monotherapy during grace period (n = 352)^
Age at time zero, mean (SD)	54.17 (12.95)	52.37 (13.31)	55.27 (12.54)
Male gender, n (%)	172 (26.1)	60 (20.9)	102 (29.0)
Race and ethnicity, n (%)			
Black, non-Hispanic	92 (14.0)	40 (13.9)	46 (13.1)
Hispanic	79 (12.0)	47 (16.4)	31 (8.8)
White, non-Hispanic	393 (59.6)	162 (56.4)	220 (62.5)
Other*	95 (14.4)	38 (13.2)	55 (15.6)
Insurance status, n (%)			
Government	248 (37.6)	108 (37.6)	128 (36.4)
Private	309 (46.9)	137 (47.7)	167 (47.4)
Uninsured or other	102 (15.5)	42 (14.6)	57 (16.2)
Year of Time Zero, mean (SD)	2014 (4)	2014 (4)	2014 (4)
Clinical variables+			
Hypertension, n (%)	150 (22.8)	87 (30.3)	76 (21.6)
Diabetes mellitus, n (%)	36 (5.5)	26 (9.1)	17 (4.8)
Other comorbidities, n (%)†	36 (5.5)	25 (8.7)	30 (8.5)
eGFR, mean (SD)	110.49 (36.04)	88.65 (20.51)	86.04 (21.84)
Total Cholesterol, mean (SD)	184.48 (20.45)	182.90 (25.22)	184.37 (24.97)

Results

Table 4. Hazard ratios, risk differences, and restricted mean survival times for 5-year risk of MACE comparing methotrexate monotherapy and addition of second-line DMARD therapy, northwestern medicine, January 2000–June 2020.

Analysis†	*Marginal HR**	*Risk Difference at month 60**	*RMST at month 60**
Main	0.717 (0.709 1.228)	-1.47 (-4.74, 1.95)	0.573 (-0.751, 1.807)
Sensitivity analyses			
12-month grace period	0.723 (0.537, 1.270)	-2.1 (-6.86, 2.54)	0.778 (-0.945, 2.508)
Linear time	1.066 (0.208, 1.123)	-0.9 (-4.49, 2.38)	0.351 (-0.884, 1.754)
Square time	0.711 (0.241, 1.107)	-1.35 (-4.64, 2.04)	0.529 (-0.773, 1.820)
Diagnosis of RA at least 6 months before time zero	0.880 (0.744, 1.330)	-0.32 (-4.14, 3.39)	0.120 (-1.238, 1.594)
HCQ excluded from DMARD	1.031 (0.695, 1.345)	-0.76 (-4.45, 3.65)	0.262 (-1.138, 1.517)

* - 95% percentile bootstrap confidence intervals (CI). Weights and outcomes models adjust for age, gender, race and ethnicity, diabetes, hypertension, and other comorbidity status, baseline cholesterol level, and baseline eGFR.

† - Model used for the denominator of the weights calculation included baseline and time-varying treatment status, comorbidity status, and laboratory values.

Discussion

- Results were contrasted with the previous observational studies where they showed 30-50% reduction in CVD events
- Aligned with the prior metanalysis that included RCTs

Limitations

- Only consisted of structured data–ICD codes and prescription data– from a single health system
- Unmeasured confounding can be subjected – unable to include clinical assessments and markers of inflammation in the models
- Care from other facilities may not be recorded in the EHR- which may affect study eligibility, treatment identification and outcome ascertainment
- MACE used all-cause death instead of CVD-specific death
- Unable to examine individual DMARDs separately due to small sample size

THANK YOU