AS Project Analysis Notes

Wednesday, June 20, 2018

# AS case definition

* Denominator
  + At least 12 months of continuous enrollment
  + For annual prevalence (calendar year), continuous enrollment for at least 6 months of the calendar year
  + For overall, 12 months of continuous enrollment can span calendar years
  + Includes 65+ year-olds
* Numerator
  + At least 2 diagnosis codes of 720.0
  + Both must be from a rheumatologist ambulatory visit
  + Both must be between 7-365 days apart
  + AS date is set as the date of the 2nd diagnosis
  + AS date must be within enrollment window (i.e., patient must also be in the denominator)
* Protocol states the numerator should be single diagnosis of 720.0, but this was considered (a posteriori) to be not specific
* We also considered broadening the scope of ICD-9 diagnosis codes to 720.xx (at least two codes); but also considered this to be not specific

# Exposure ascertainment

* Follows protocol
* But DMARD, NSAID, and no exposure episodes are grouped together into a “no TNF” exposure category
* Comparisons are made between 2 groups: TNF vs no TNF (DMARD, NSAID, or no exposure)

# Prevalent condition ascertainment

* 12-month period prevalence (±6 months from exposure date)
  + Other time windows were calculated but only 12-month is reported

# Propensity score model

* Model was a logistic regression model
* TNF exposure was used as the reference exposure
* Model output is probability of exposure to TNF
* Model estimation performed separately for the 3 data sources: MPCD, Marketscan, and Medicare
* Inverse probability treatment weight (IPTW) for TNF exposure
* IPTW are stabilized to reduce oversized effect of large propensity scores
* The common support region lower bound is the maximum of the lowest TNF propensity score among the 2 exposure groups. The common support region upper bound is the minimum of the greatest TNF propensity score among the 2 exposure groups

# Incident outcome modeling

* Subjects with disease prior to exposure are excluded
  + Exception for hospitalized and opportunistic infections, and non-melanoma skin cancer
* Models are weighted using IPTW
* Subjects with propensity scores outside of common support region are excluded
* Additional covariates include
  + 6-month mean daily corticosteroid dose (5 level ordinal)
* Comparisons are between
  + TNF vs DMARD, NSAID, or no exposure

# Tables

Data in tables below do not reflect pending changes described in comment margins above.

## Prevalence of AS

Denominator:

* At least 12 months of continuous enrollment
* For annual prevalence, continuous enrollment for at least 6 months of the year
* For overall, 12 months of continuous enrollment can span calendar year
* Includes 65+ year-olds
* Excludes <65 year-olds

Numerator:

* At least 2 diagnosis codes of 720.0
* Both must be from a rheumatologist ambulatory visit
* Both must be between 7-365 days apart
* AS date is set as the date of the 2nd diagnosis
* AS date must be within enrollment window (i.e., patient must also be in the denominator)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **year** | **numer5pct** | **denom5pct** | **numerEstimated** | **denomEstimated** | **prev** |
| 2006 | 37 | 637,960 | 740 | 12,759,200 | 0.006% |
| 2007 | 67 | 687,896 | 1,340 | 13,757,920 | 0.010% |
| 2008 | 90 | 687,227 | 1,800 | 13,744,540 | 0.013% |
| 2009 | 117 | 687,127 | 2,340 | 13,742,540 | 0.017% |
| 2010 | 143 | 695,742 | 2,860 | 13,914,840 | 0.021% |
| 2011 | 178 | 719,161 | 3,560 | 14,383,220 | 0.025% |
| 2012 | 214 | 756,610 | 4,280 | 15,132,200 | 0.028% |
| 2013 | 281 | 871,076 | 5,620 | 17,421,520 | 0.032% |
| 2014 | 328 | 873,627 | 6,560 | 17,472,540 | 0.038% |
| OVERALL 2006-2014 | 218 | 1,212,058 | 4,360 | 24,241,160 | 0.018% |

Differences from earlier estimates

* Numerator used single diagnosis code of 720.0 (determined to have low specificity)
* Numerator used 2 diagnosis codes of 720.xx (determined to have low specificity)

## Demographic characteristics

AS and non-AS cohorts

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **cohort** | **database** | **denom** | **age** | **female** |
| AS | MPCD | 2,855 | 43.3 (13.5) | 35.5% (n = 1,013) |
| AS | Marketscan | 12,566 | 45.7 (13.4) | 41.0% (n = 5,155) |
| AS | Medicare | 4,637 | 71.9 (5.8) | 38.8% (n = 1,801) |
| Non-AS | MPCD | 1,139,225 | 50.1 (16.6) | 55.8% (n = 635,972) |
| Non-AS | Medicare | 1,447,192 | 74.5 (8.3) | 64.4% (n = 931,837) |

Exposed among AS cohort

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **cohort** | **database** | **denom** | **age** | **female** |
| Exposed | MPCD | 1,223 | 45.1 (14.2) | 38.0% (n = 465) |
| Exposed | Marketscan | 5,205 | 45.4 (13.7) | 45.1% (n = 2,350) |
| Exposed | Medicare | 2,666 | 72.3 (5.8) | 40.8% (n = 1,087) |
| Non-AS | MPCD | 1,139,225 | 50.1 (16.6) | 55.8% (n = 635,972) |
| Non-AS | Medicare | 1,447,192 | 74.5 (8.3) | 64.4% (n = 931,837) |

Exposure cohorts

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **database** | **exposure** | **denom** | **age** | **female** |
| MPCD | DMARD | 145 | 43.7 (15.0) | 42.1% (n = 61) |
| MPCD | NSAID | 265 | 43.6 (12.7) | 46.8% (n = 124) |
| MPCD | No exposure | 512 | 50.9 (13.9) | 34.6% (n = 177) |
| MPCD | TNF | 575 | 40.8 (12.7) | 37.4% (n = 215) |
| Marketscan | DMARD | 710 | 46.2 (13.2) | 54.9% (n = 390) |
| Marketscan | NSAID | 1,293 | 45.8 (14.0) | 47.8% (n = 618) |
| Marketscan | No exposure | 1,699 | 47.3 (14.6) | 40.5% (n = 688) |
| Marketscan | TNF | 2,864 | 43.8 (13.1) | 45.0% (n = 1,290) |
| Medicare | DMARD | 550 | 71.8 (5.3) | 50.2% (n = 276) |
| Medicare | NSAID | 1,108 | 72.1 (5.7) | 41.5% (n = 460) |
| Medicare | No exposure | 1,244 | 73.1 (6.3) | 36.0% (n = 448) |
| Medicare | TNF | 702 | 70.9 (4.9) | 42.5% (n = 298) |

## Prevalence of comorbidities

12-month prevalence

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **outcomeCategory** | **disease** | **MPCD AS cohort**  **N = 2,855** | **Marketscan AS cohort**  **N = 12,566** | **Medicare AS cohort**  **N = 11,699** |
| Cancer | Hematologic Cancer | 0.2 (0.1-0.7) | 0.3 (0.2-0.5) | 1.4 (1.0-1.8) |
| Cancer | Non Melanoma Skin Cancer | 0 | 0.6 (0.4-0.8) | 1.8 (1.4-2.4) |
| Cancer | Solid Cancer | 3.0 (2.2-4.1) | 2.6 (2.2-3.1) | 13.5 (12.2-14.8) |
| Cardiac disease | Aortic Insufficiency/Aortic Regurgitation | 1.8 (1.2-2.7) | 1.1 (0.8-1.4) | 6.0 (5.1-7.0) |
| Cardiac disease | Conduction Block | 0.4 (0.2-0.9) | 0.8 (0.6-1.1) | 4.2 (3.5-5.0) |
| Cardiac disease | Myocardial infarction | 0.1 (0.0-0.4) | 0.2 (0.1-0.3) | 1.1 (0.7-1.5) |
| Infection | Hospitalized infection | 0.7 (0.3-1.2) | 2.6 (2.2-3.1) | 7.9 (6.9-9.0) |
| Infection | Opportunistic infection | 0.9 (0.5-1.6) | 1.0 (0.7-1.3) | 2.1 (1.6-2.7) |
| Inflammatory bowel disease | Crohn’s Disease | 3.2 (2.3-4.3) | 3.5 (3.0-4.0) | 3.3 (2.6-4.0) |
| Inflammatory bowel disease | Ulcerative Colitis | 2.6 (1.8-3.6) | 2.3 (1.9-2.7) | 2.2 (1.7-2.8) |
| Kidney disease | Amyloidosis | 0.1 (0.0-0.4) | 0.0 (0.0-0.1) | 0.1 (0.0-0.2) |
| Kidney disease | IgA nephropathy | 0.3 (0.1-0.8) | 0.2 (0.1-0.3) | 0.0 (0.0-0.1) |
| Kidney disease | Nephrotic syndrome | 0.1 (0.0-0.4) | 0.0 (0.0-0.1) | 0.3 (0.1-0.5) |
| Lung disease | Apical Pulmonary fibrosis | 0.0 (0.0-0.2) | 0 | 0 |
| Lung disease | Interstitial lung disease | 0 | 0.1 (0.0-0.2) | 0.3 (0.2-0.6) |
| Lung disease | Restrictive lung disease | 0.8 (0.4-1.4) | 0.8 (0.6-1.1) | 3.5 (2.8-4.2) |
| Neurological Disease | Cauda Equina syndrome | 0.1 (0.0-0.4) | 0.0 (0.0-0.1) | 0.2 (0.1-0.5) |
| Neurological Disease | Spinal Cord compression | 0.1 (0.0-0.4) | 0.1 (0.0-0.2) | 0.2 (0.1-0.4) |
| Osteoporotic fracture | Clinical vertebral fracture | 1.2 (0.7-2.0) | 0.7 (0.5-0.9) | 2.6 (2.0-3.2) |
| Osteoporotic fracture | Non-vertebral osteoporotic fracture | 1.8 (1.2-2.7) | 0.9 (0.6-1.1) | 3.5 (2.8-4.2) |
| PsO/PsA | Psoriasis | 2.0 (1.3-2.9) | 3.1 (2.6-3.5) | 2.8 (2.2-3.5) |
| PsO/PsA | Psoriatic arthritis | 3.3 (2.4-4.4) | 3.9 (3.4-4.5) | 4.7 (3.9-5.5) |
| Uveitis | Uveitis | 8.1 (6.7-9.7) | 8.2 (7.5-9.0) | 5.3 (4.5-6.2) |

## Crude incidence

* Subjects with disease prior to exposure are excluded
  + Exception for hospitalized and opportunistic infections, and non-melanoma skin cancer

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **type** | **outcomeCategory** | **disease** | **MPCD**  **TNF** | **MPCD**  **DMARD, NSAID, or no exposure** | **Marketscan**  **TNF** | **Marketscan**  **DMARD, NSAID, or no exposure** | **Medicare**  **TNF** | **Medicare**  **DMARD, NSAID, or no exposure** |
| Comorbidity | Cancer | Hematologic Cancer | 0.14 (0.00-0.79) | 0.40 (0.11-1.02) | 0.12 (0.04-0.29) | 0.46 (0.27-0.73) | 0.79 (0.49-1.20) | 0.48 (0.34-0.64) |
| Comorbidity | Cancer | Non Melanoma Skin Cancer | 1.43 (0.69-2.63) | 1.21 (0.62-2.11) | 0.94 (0.66-1.29) | 0.90 (0.62-1.25) | 3.27 (2.59-4.06) | 3.13 (2.76-3.54) |
| Comorbidity | Cancer | Solid Cancer | 1.45 (0.70-2.67) | 3.43 (2.36-4.82) | 1.36 (1.02-1.77) | 2.38 (1.91-2.93) | 3.33 (2.62-4.18) | 5.22 (4.71-5.78) |
| Comorbidity | Cardiac disease | Aortic Insufficiency/Aortic Regurgitation | 0.71 (0.23-1.65) | 1.22 (0.63-2.13) | 0.47 (0.28-0.73) | 0.67 (0.44-0.98) | 2.34 (1.77-3.04) | 2.71 (2.36-3.10) |
| Comorbidity | Cardiac disease | Conduction Block | 0.28 (0.03-1.02) | 0.90 (0.41-1.72) | 0.59 (0.38-0.88) | 0.98 (0.69-1.34) | 2.08 (1.55-2.72) | 2.63 (2.29-3.00) |
| Comorbidity | Cardiac disease | Myocardial infarction | 0.42 (0.09-1.24) | 0.00 (0.00-0.37) | 0.22 (0.10-0.42) | 0.20 (0.09-0.40) | 0.79 (0.49-1.21) | 0.94 (0.75-1.17) |
| Comorbidity | Infection | Hospitalized infection | 3.04 (1.88-4.64) | 1.82 (1.08-2.87) | 5.41 (4.70-6.19) | 5.00 (4.31-5.77) | 8.42 (7.25-9.71) | 9.29 (8.62-10.01) |
| Comorbidity | Infection | Opportunistic infection | 0.85 (0.31-1.85) | 0.70 (0.28-1.45) | 1.56 (1.20-2.00) | 1.24 (0.91-1.64) | 1.67 (1.21-2.25) | 1.92 (1.64-2.24) |
| Comorbidity | Kidney disease | Amyloidosis | 0.00 (0.00-0.52) | 0.30 (0.06-0.87) | 0.02 (0.00-0.14) | 0.00 (0.00-0.09) | 0.04 (0.00-0.20) | 0.04 (0.01-0.11) |
| Comorbidity | Kidney disease | IgA nephropathy | 0.14 (0.00-0.79) | 0.10 (0.00-0.55) | 0.07 (0.02-0.21) | 0.08 (0.02-0.22) | 0.11 (0.02-0.32) | 0.06 (0.02-0.13) |
| Comorbidity | Kidney disease | Nephrotic syndrome | 0.28 (0.03-1.02) | 0.00 (0.00-0.37) | 0.05 (0.01-0.18) | 0.05 (0.01-0.18) | 0.07 (0.01-0.27) | 0.04 (0.01-0.11) |
| Comorbidity | Lung disease | Apical Pulmonary fibrosis | 0.00 (0.00-0.52) | 0.10 (0.00-0.55) | 0.00 (0.00-0.09) | 0.00 (0.00-0.09) | 0.00 (0.00-0.14) | 0.00 (0.00-0.04) |
| Comorbidity | Lung disease | Interstitial lung disease | 0.00 (0.00-0.52) | 0.00 (0.00-0.37) | 0.07 (0.02-0.21) | 0.03 (0.00-0.14) | 0.45 (0.23-0.78) | 0.25 (0.15-0.37) |
| Comorbidity | Lung disease | Restrictive lung disease | 0.57 (0.16-1.46) | 1.00 (0.48-1.84) | 0.59 (0.38-0.88) | 0.64 (0.42-0.95) | 1.73 (1.26-2.33) | 1.69 (1.43-2.00) |
| Comorbidity | Neurological Disease | Cauda Equina syndrome | 0.00 (0.00-0.52) | 0.10 (0.00-0.55) | 0.02 (0.00-0.14) | 0.00 (0.00-0.09) | 0.04 (0.00-0.20) | 0.06 (0.02-0.13) |
| Comorbidity | Neurological Disease | Spinal Cord compression | 0.00 (0.00-0.52) | 0.10 (0.00-0.55) | 0.24 (0.12-0.45) | 0.25 (0.12-0.47) | 0.07 (0.01-0.27) | 0.17 (0.09-0.28) |
| Comorbidity | Osteoporotic fracture | Clinical vertebral fracture | 0.71 (0.23-1.65) | 0.60 (0.22-1.31) | 0.37 (0.21-0.61) | 0.62 (0.39-0.92) | 1.63 (1.18-2.21) | 1.75 (1.48-2.06) |
| Comorbidity | Osteoporotic fracture | Non-vertebral osteoporotic fracture | 1.43 (0.68-2.62) | 2.03 (1.24-3.14) | 1.15 (0.84-1.53) | 1.01 (0.72-1.37) | 1.99 (1.47-2.62) | 2.26 (1.95-2.61) |
| Disease manifestation | Inflammatory bowel disease | Crohn’s Disease | 1.94 (1.03-3.32) | 1.43 (0.78-2.40) | 1.67 (1.29-2.13) | 1.42 (1.06-1.85) | 0.83 (0.51-1.27) | 0.55 (0.41-0.73) |
| Disease manifestation | Inflammatory bowel disease | Ulcerative Colitis | 0.73 (0.24-1.70) | 0.81 (0.35-1.59) | 1.38 (1.04-1.80) | 1.11 (0.81-1.50) | 1.03 (0.67-1.51) | 0.60 (0.44-0.78) |
| Disease manifestation | PsO/PsA | Psoriasis | 1.88 (1.00-3.22) | 0.91 (0.42-1.73) | 2.06 (1.64-2.56) | 1.41 (1.06-1.84) | 1.26 (0.86-1.78) | 0.80 (0.62-1.01) |
| Disease manifestation | PsO/PsA | Psoriatic arthritis | 2.52 (1.47-4.04) | 1.11 (0.56-1.99) | 2.19 (1.75-2.71) | 1.36 (1.02-1.78) | 1.32 (0.91-1.86) | 0.57 (0.42-0.75) |
| Disease manifestation | Uveitis | Uveitis | 2.60 (1.51-4.16) | 4.22 (3.00-5.76) | 3.58 (3.00-4.24) | 3.78 (3.17-4.47) | 1.61 (1.14-2.20) | 1.12 (0.90-1.37) |



## Hazard ratios

* Weighted using stabilized IPTW and adjusted for 6-month prednisone equivalent daily dose
* Comparisons are between
  + TNF vs DMARD, NSAID, or no exposure
* Only HRs significantly different from 1.0 are shown
* Full results for all outcomes and all models are in the Excel spreadsheet **phregHazardRatios.xlsx**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **disease** | **database** | **nTNF** | **nComparator** | **HazardRatio** | **RobustWaldLower** | **RobustWaldUpper** |
| Hospitalized infection | MPCD | 539 | 748 | 4.15 | 1.88 | 9.15 |
| Psoriatic arthritis | MPCD | 521 | 739 | 3.40 | 1.23 | 9.39 |
| Psoriatic arthritis | Medicare | 669 | 2,187 | 2.04 | 1.25 | 3.33 |
| Ulcerative Colitis | Medicare | 680 | 2,210 | 1.81 | 1.06 | 3.11 |
| Hematologic Cancer | Medicare | 700 | 2,223 | 1.79 | 1.02 | 3.13 |
| Solid Cancer | MPCD | 532 | 742 | 0.44 | 0.20 | 0.97 |
| Hematologic Cancer | Marketscan | 2,852 | 3,137 | 0.22 | 0.07 | 0.64 |