Collaborating with Real-World Data Scientists to Assess the Incidence of Safety Events in Patients with Giant Cell Arteritis

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Outline

- Introduction to the **problem**
- **Methods** of data collection
  - Clinical Trials
  - Healthcare Claims Database
- **Comparing** Clinical and Real World Safety Data
  - Comparison of safety data – **Clinical Trials**
  - Comparison of safety data **- Healthcare Claims Database**
  - **Risk Ratios** from the Claims Database
  - **Conclusions** & **Limitations**
- Additional work
  - Using safety data to assess the **steroid burden**

The problem

Giant Cell Arteritis (GCA) is a rare disease that predominantly occurs in elderly patients

- Peak of onset is in 8th decade
- Patient population has more comorbidities than younger RA patients

The safety "problem"

- Necessary to compare safety of TCZ in GCA to RA
- Safety profile of TCZ in patients with GCA may differ from that observed in patients with RA due to differences in the underlying disease and the higher dosing of GCs used to treat GCA
  - ➢ Expected a higher number of AEs than we're used to seeing on TCZ (sicker, older, higher steroid use)

Objective:

Evaluate incidence rates (IRs) of safety events in GCA patients in both the real world setting and clinical study setting to contextualize the observed safety profile of TCZ in GCA

Methods of Data Collection - *Clinical Trials*

Pooled population of RA patients and GCA patients who received TCZ in clinical trials

- Patients enrolled in TCZ clinical trials in RA met the following criteria:
  - Age ≥ 18 years
  - Active RA with ≥ 4 swollen and ≥ 4 tender joints
- Patients enrolled in TCZ clinical trials in GCA met the following criteria:
  - Age ≥ 50 years
  - Diagnosis of new onset or relapsing GCA
  - GCA diagnosis confirmed by temporal artery biopsy and/or cross-sectional imaging

Incidence rates of adverse events of special interest (AESI) associated with TCZ were calculated

- AESI's are identified and potential risks observed during the TCZ clinical trial program (e.g. infections, hepatic events, GI perforation, demyelination, cardiovascular events, bleeding events and malignancies)
- Analysis:
  - AE rates per 100 patient-years exposure (number of events/total study duration, multiplied by 100)

Methods of Data Collection - *Healthcare Claims Database*

US-based MarketScan® administrative healthcare claims database was used to estimate AESI incidence rates in TCZ-naïve adult patients with GCA or RA

Stringent criteria used to identify patient records to be used from the claims database with an aim to match the RA and GCA populations enrolled in clinical trials as closely as possible

- Criteria focused on:
  - Minimum numbers of inpatient/outpatient claims with specific RA/GCA diagnosis
  - Aged ≥ 50 years at index date
  - No TCZ exposure within the patient's enrollment in the database
  - Minimum prescription claims for specific GCA/RA-related medications & Diagnostic work-up claims (GCA)
  - Minimum eligibility period prior to index date and follow up after index date

Risks Ratios for Adverse Events of Special Interest (AESI) for GCA vs RA were adjusted for age and oral GC use and estimated using Poisson regression

Populations – Clinical Trials & Healthcare Database

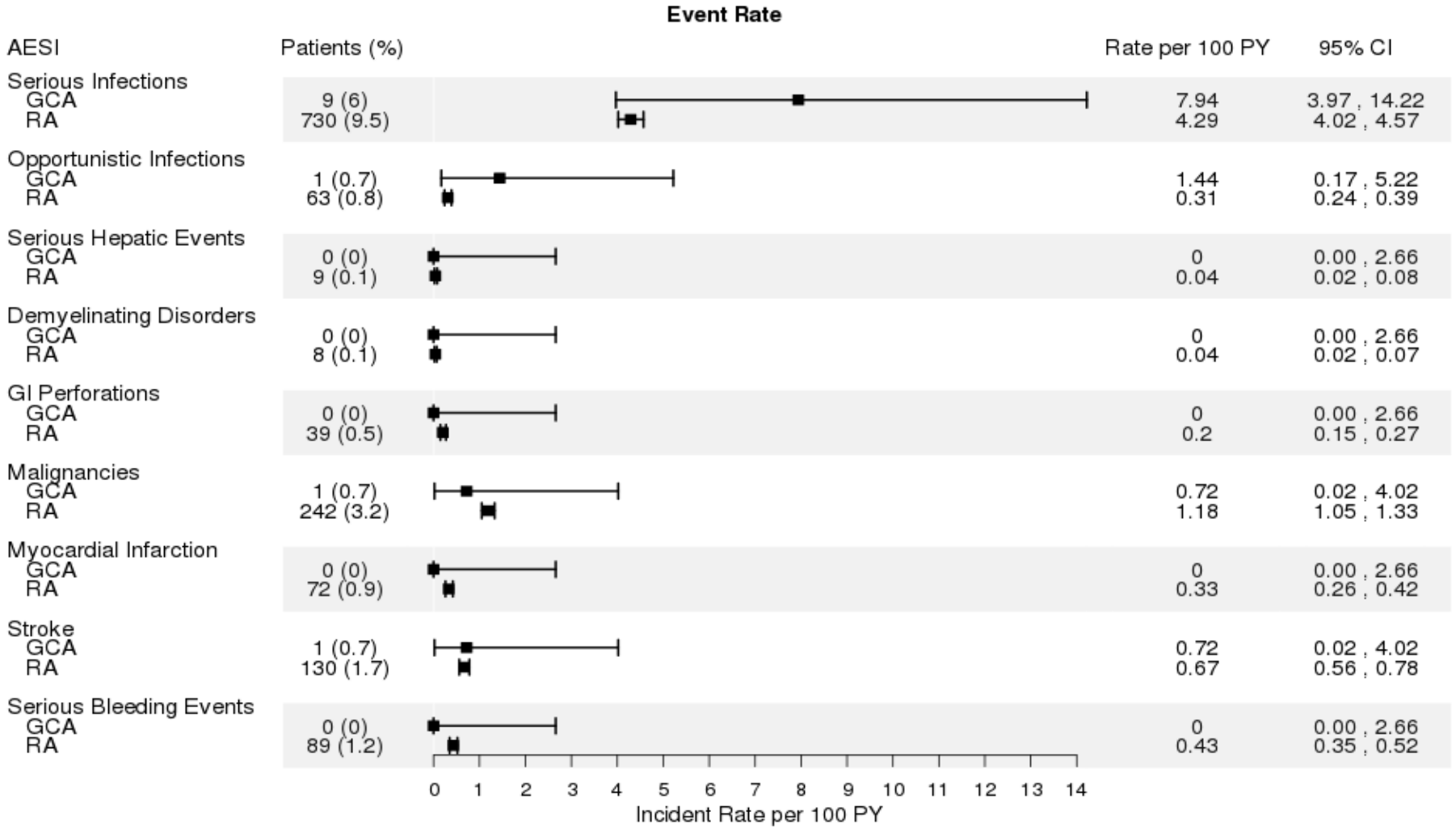
- GCA trial patients generally older with much higher GC use than RA trial patients
- Higher GC use in Healthcare Claims Database compared to Clinical Database, both for GCA and RA

	GCA Clinical Trial	RA Clinical Trial Database	Healthcare Claims Analysis	
	Patients With GCA (n=149)	Patients With RA (n=7,647)	Patients With GCA (n=4,804)	Patients With RA (n=15,164)
TCZ exposure	Yes	Yes	No	No
Age, mean (SD), years	69.5 (8.4)	52 (12.6)	73.4 (9.8)	60.3 (8.2)
<65 years, n (%)	49 (33)	6438 (84)	1096 (23)	11411 (75)
≥65 years, n (%)	100 (67)	1209 (16)	3708 (77)	3753 (25)
Female, n (%)	112 (75)	6240 (82)	3425 (71)	10721 (71)
Duration of disease, years*	0.8 (1.5)	8.1 (8.4)	1.9 (2.1)	4.3 (2.9)
Follow-up, mean (SD), years	0.9 (0.2)	2.9 (1.9)	3.9 (3.1)	4.5 (2.8)
Patients receiving GCs, n (%)	149 (100)	4161 (54)	4804 (100)	12705 (84)
Baseline GC dose, mean (SD),mg	35 (13.5)	8.6 (55.5)	46.9 (34.8)	NA
Cumulative GC dose†	(n=149)	NA	(n=3608)	(n=8894)
Mean (SD) mg	2213 (1467)	NA	2480 (-4569)	1329 (4382)
<1000 mg, n (%)	28 (19)	NA	228 (-5)	6366 (42)
≥1000 mg, n (%)	121 (81)	NA	4576 (-95)	8798 (58)

* For claims cohorts, duration was defined as the time from the index date to last claim with a diagnosis of the disease.
† For the GCA trial, cumulative GC dose was on-study GC use only; for claims cohorts, cumulative GC dose was calculated from index date throughout entire follow-up period.

Safety in Clinical Trials – RA vs GCA

- TCZ-treated patients in the GCA trial had greater incidence of serious infections and opportunistic infections than TCZ-treated patients in the pooled RA clinical trial population

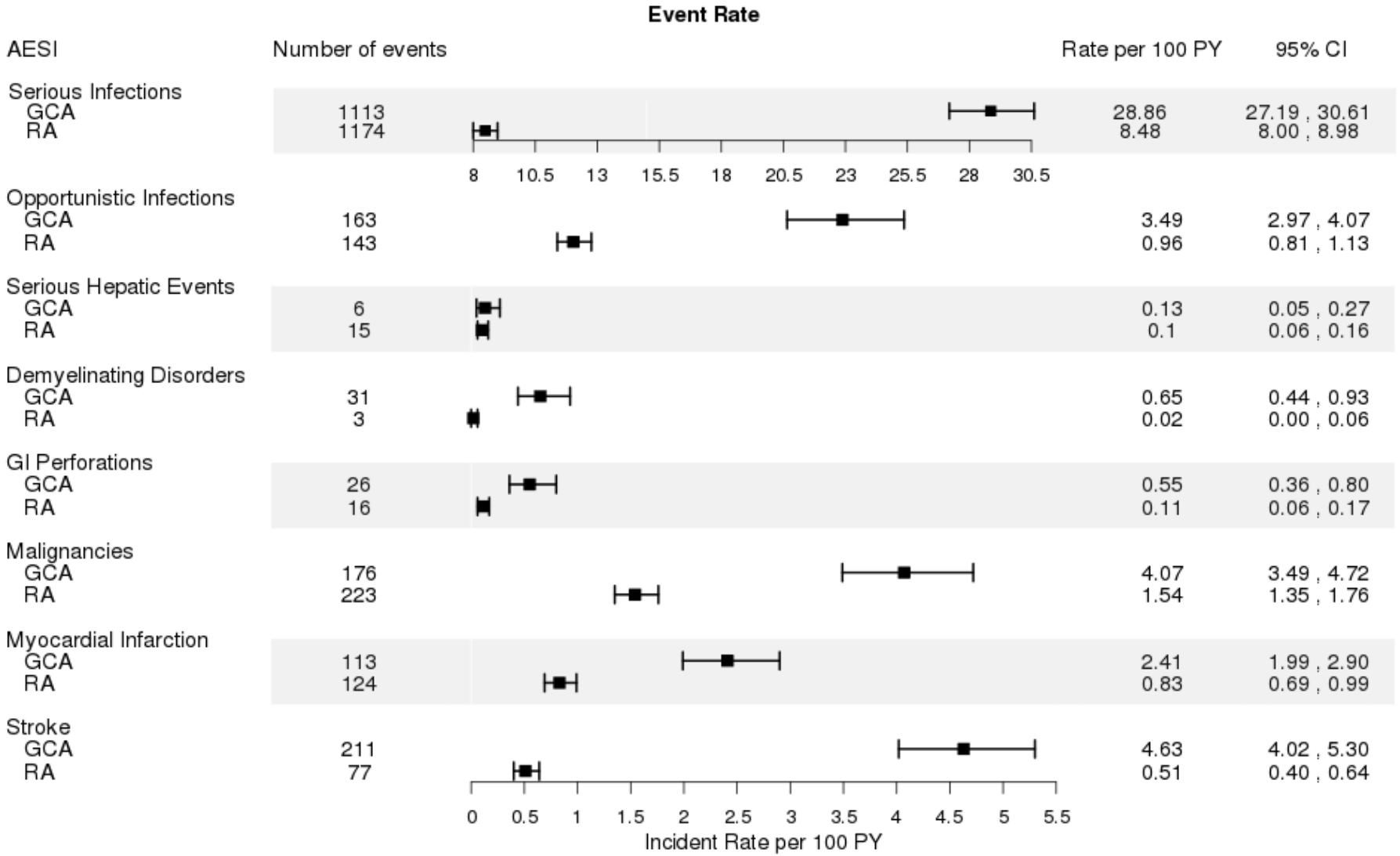


TCZ Patients With GCA:
n = 149
PY ≈ 138

TCZ Patients With RA:
n = 7,647
PY ≈ 22,394

Healthcare Claims Database – GCA vs RA

- IRs of AESI's in TCZ-naïve patients with GCA exceeded the IRs of AESI in TCZ-naïve patients with RA from healthcare claims data

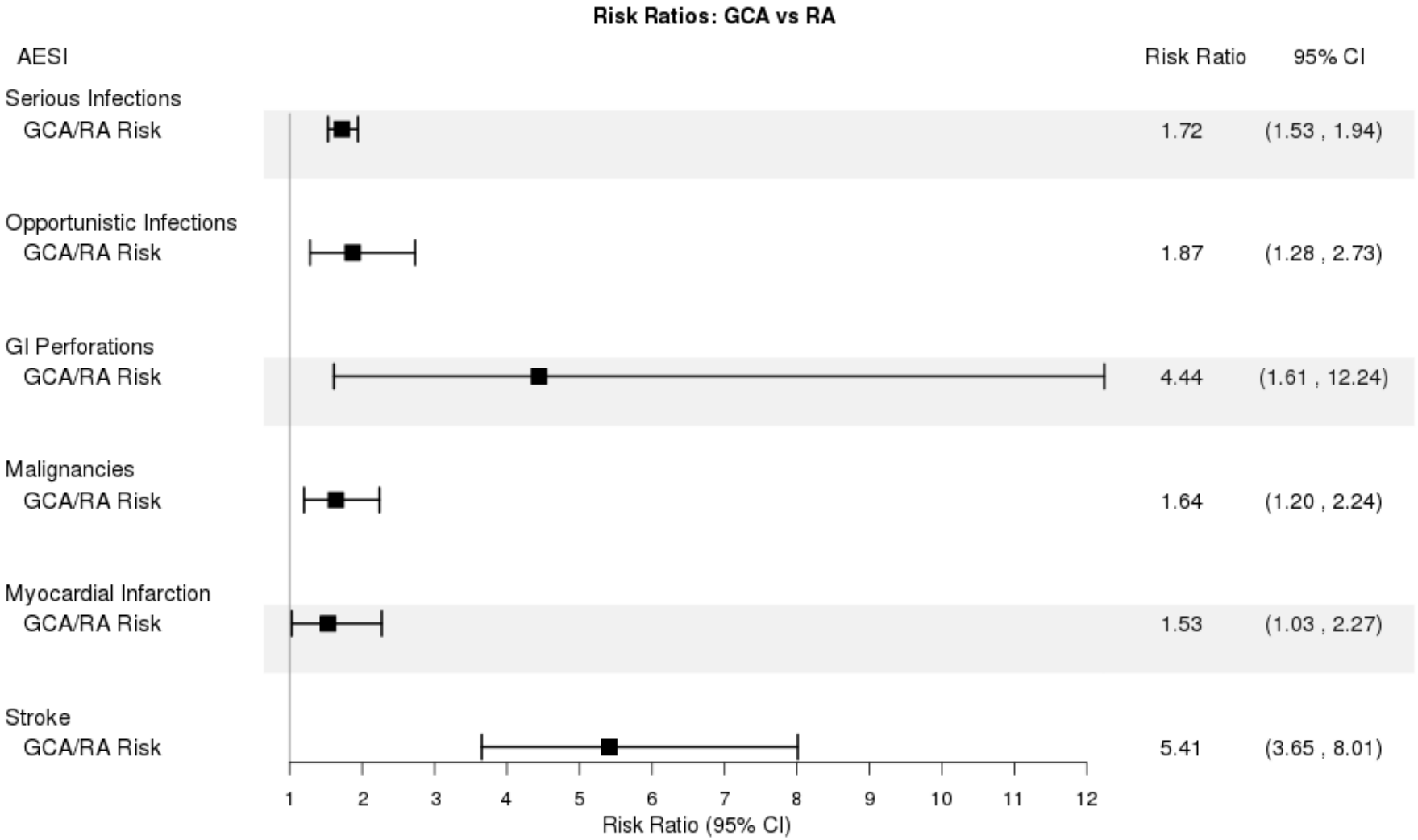


MarketScan Patients With GCA:
n = 4,804
PY ≈ 4,804

MarketScan Patients With RA:
n = 15,164
PY ≈ 15,164

Healthcare Claims Database - Risk Ratios

- After adjusting for age and oral GC dose, TCZ-naive patients with GCA in the US claims database were at higher risk for all AESI (with sufficient data) compared with TCZ-naïve patients with RA



Conclusions & Limitations

Conclusions

- Higher AESI IRs observed in GCA compared to RA in the healthcare claims database, which is consistent with clinical trial safety observations
- Suggests the use of higher doses and longer courses of GCs in GCA compared with RA appears to influence the incidence of AESI in both TCZ-naïve and TCZ-treated patients.

Limitations

- Limited data availability from Healthcare Claims databases
  - Clinical data points are not typically collected in claims databases and few patient demographic variables are available
- Non-random sampling
  - MarketScan data comprise only commercially insured individuals (i.e. from large companies)
- Number of treated GCA patients in clinical trials
  - Number of TCZ-treated patients with GCA much smaller than number of TCZ-treated patients with RA. Hence, PYE is small for the TCZ-treated GCA cohort

Additional work: Using safety data to assess the steroid burden

- A separate analysis was conducted to evaluate the **steroid burden** in GCA patients
  - Reducing the steroid burden is an additional efficacy outcome
  - Objective: determine the GC exposure and risk of GC-related AEs in real-world patients with GCA
- Retrospective analysis of patients ≥50 yrs with GCA
  - Data from the Truven Healthcare MarketScan database (USA) and Clinical Practice Research Datalink (CPRD, UK)
- Outcomes: oral GC use (cumulative prednisone-equivalent exposure), GC-related AEs and the association of AE risk with GC exposure over 52 weeks
- Logistic regression and Cox proportional hazards models used to analyse AE risk based on GC use over time
  - Risk of AE associated with a 1g increase in cumulative CS exposure

Additional work: Using safety data to assess the steroid burden (2)

- 4,804 patients in the US MarketScan® database and 3,973 patients in the UK CPRD database included
  - Median starting GC dose 20–50 mg/day
  - Cumulative GC dose at 52 weeks 4000–4800 mg
- Within 52 weeks of diagnosis, likelihood of a GC-related AE was **significantly increased** for each 1g increase in cumulative GC dose
  - US cohort: Odds Ratio=1.17 [95% CI: 1.063,1.287]
  - UK cohort: Odds Ratio=1.06 [95% CI: 1.03, 1.09]
- **Conclusions**
  - In real-world patients with GCA, increased cumulative GC exposure was associated with an increased risk of GC-related AEs
  - Safety data can also be used as supporting evidence of efficacy

Broder MS, et al. Corticosteroid-related adverse events in patients with giant cell arteritis: A claims-based analysis. Semin Arthritis Rheum 2016; 46: 246-52.
Gale S, et al. Risk associated with cumulative oral glucocorticoid use in patients with giant cell arteritis in real-world databases from the USA and UK. Rheumatol Ther 2018.

Doing now what patients need next

Inclusion criteria for MarketScan® analysis
RA Patients

- ≥ 2 outpatient confirmatory claims (separated by ≥ 7 days and ≤ 365 days) with an RA diagnosis or ≥ 1 inpatient confirmatory claim. The index date was defined as the first date of RA diagnosis
- Age ≥ 50 years at index date
- Continuous medical and pharmacy coverage and data available for ≥ 365 days (30-day gap permitted only in the pre-index period)
- ≥ 1 prescription claim for a conventional synthetic disease-modifying antirheumatic drug or for a biologic disease-modifying antirheumatic drug (adalimumab, certolizumab, etanercept, golimumab, infliximab, abatacept, tofacitinib) after the index date and during the continuous enrollment period
- No concomitant rheumatologic or other immunologic conditions or GCA (defined as ≥ 2 outpatient claims [separated by ≥ 7 days and ≤ 365 days] or ≥ 1 inpatient claim) before the end of the continuous enrollment period
- No TCZ exposure within the patient's enrollment in the database

Inclusion criteria for MarketScan® analysis
GCA Patients

- ≥ 1 inpatient claim or ≥ 2 outpatient claims (separated by ≥ 7 days and ≤ 365 days) with a GCA diagnosis (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 446.5). The index date was defined as the first date of GCA diagnosis
- Age ≥ 50 years at index date
- ≥ 2 prescription claims for oral GCs (the first claim ≤ 6 months after diagnosis, the second claim ≤ 6 months after the first)
- ≥ 1 diagnostic work-up claim (≤ 1 year pre- or post-index) for temporal artery biopsy (CPT: 37609); magnetic resonance angiography, computed tomography angiography; or positron emission tomography/computed tomography
- No prior claims with a GCA diagnosis (≤ 1 year pre-index date)
- ≥ 1 claim with a GCA diagnosis after the diagnostic work-up claim
- Continuous medical and pharmacy coverage and data available (30-day gap permitted only in the pre-index period)
- ≥ 365 days eligibility prior to index date
- No TCZ exposure within the patient's enrollment in the database
- ≥ 365 days of follow-up after index date and after date of first GC prescription