Drug-related pancytopenia and leukopenia in rheumatoid arthritis: Are all csDMARDs equal?

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Background

- Cytopenia is a known side-effect of csDMARDs in RA.
- Leukopenia and pancytopenia may increase the risk for serious infections.
- Rheumatologists and GPs routinely order full blood counts for all patients.
- However, the risk of cytopenia may differ across csDMARDs, and laboratory testing may not be needed for all.

Objectives

- To assess the **comparative risk of leukopenia and pancytopenia** for the most frequently used first-line csDMARDs in RA:
  - **methotrexate (MTX),**
  - **hydroxychloroquine (HCQ),**
  - **sulphasalazine (SSZ), and**
  - **leflunomide (LEF).**

Methods

- Data from **7 databases** from 4 countries:
  - CCAE, MDCR, Optum, IQVIA Ambulatory EMR (**US**)
  - IQVIA THIN IMRD EMR (**UK**)
  - IQVIA Disease Analyzer EMR (**Germany**)
  - SIDIAP (**Spain**).
- Cohorts included adult patients with RA from 2005-19
  - with at least one-year prior follow-up,
  - no prior inflammatory arthritis,
  - initiation of first-line csDMARD, and
  - no cytopenia in the preceding 30 days.
- Participants were followed from one day after treatment initiation to the earliest of
  - event occurrence,
  - treatment discontinuation/switching plus
    - 14 days in the on-treatment analysis,
    - five years in the intent-to-treat (ITT) analysis,
  - or loss to follow-up.
- **MTX was used as reference group**.
- Cox models were fitted with propensity score stratification for observed confounding and negative control outcomes calibration for residual error.
- Estimates across database were pooled where I^2<40% was seen.

- A total of **166,347 patients** informed the analyses.
- Pooled incidence rate of leukopenia for MTX was **10.9 per 1,000 person years**
- Pooled incidence rate of pancytopenia for MTX and **3.2 per 1,000 person years**

MTX was used as reference group

- The results for comparisons for the different databases and pooled estimates where applicable show that MTX has slightly higher hazards of leukopenia and of pancytopenia compared to LEF but no consistently differential risks compared to HCQ or SSZ. On-treatment and ITT analyses yielded similar results.

Pancytopenia and leukopenia are rare side-effects of csDMARDs, apparently more frequent with MTX and less with LEF

Prior full blood counts were inconsistently obtained in fewer than 50% of csDMARD new users (e.g. more frequent in MTX [42%] than HCQ [32%] in CCAE and Optum; roughly equal in MDCR), these results should inform future monitoring recommendations.

Figure 1. Calibrated hazard ratios (95% CI) vs MTX, on-treatment analysis

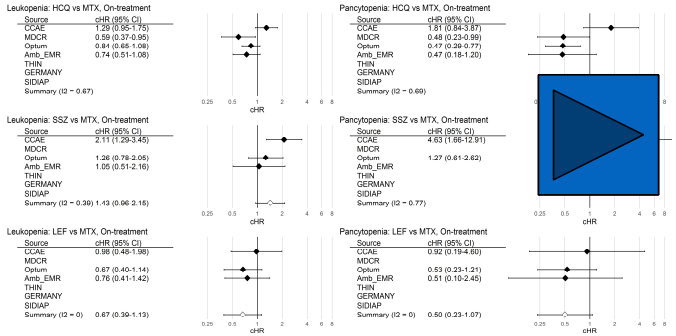
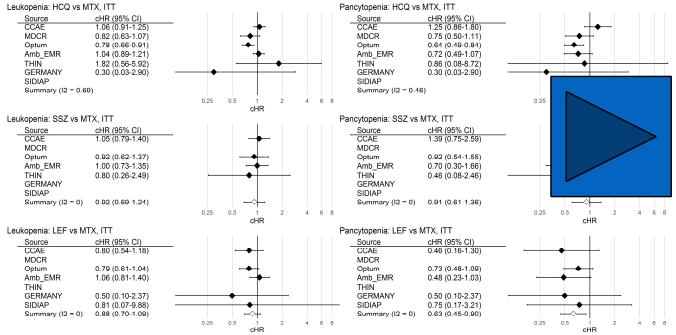


Figure 2. Calibrated hazard ratios (95% CI) vs MTX, ITT analysis

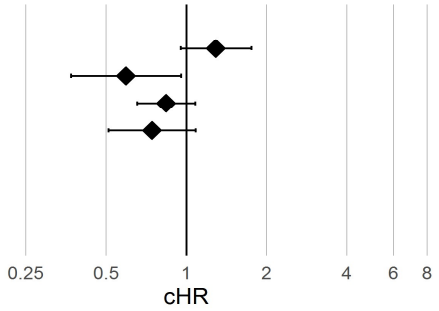


Database estimates not reported where adequate covariate balance not attained. Meta-analysis results not reported where I2>0.4. CI: Confidence Interval; MTX: Methotrexate; HCQ: Hydroxychloroquine; SSZ: sulphasalazine; LEF: Leflunomide; CCAE: IBM MarketScan Commercial Claims and Encounters (US); MDCR: IBM MarketScan Medicare Supplemental Beneficiaries (US); Optum: Optum de-identified Clinformatics Datamart (US); Amb_EMR: IQVIA Ambulatory EMR (US); THIN: The Health Improvement Network (UK); GERMANY: IQVIA Disease Analyzer EMR (Germany).

Figure 1. Calibrated hazard ratios (95% CI) vs MTX, on-treatment analysis

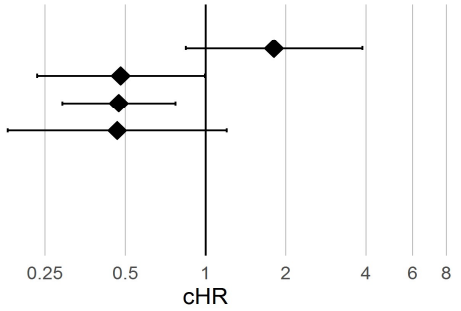
Leukopenia: HCQ vs MTX, On-treatment

Source	cHR (95% CI)
CCAE	1.29 (0.95-1.75)
MDCR	0.59 (0.37-0.95)
Optum	0.84 (0.65-1.08)
Amb_EMR	0.74 (0.51-1.08)
THIN	
GERMANY	
SIDIAP	
Summary (I2 = 0.67)	



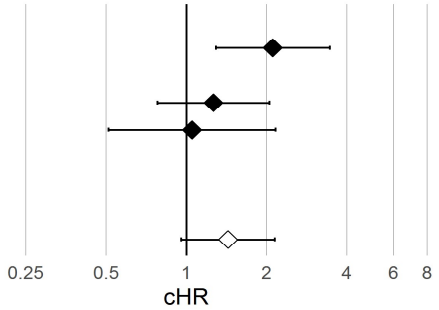
Pancytopenia: HCQ vs MTX, On-treatment

Source	cHR (95% CI)
CCAE	1.81 (0.84-3.87)
MDCR	0.48 (0.23-0.99)
Optum	0.47 (0.29-0.77)
Amb_EMR	0.47 (0.18-1.20)
THIN	
GERMANY	
SIDIAP	
Summary (I2 = 0.69)	



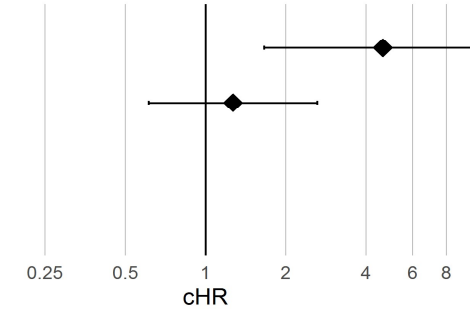
Leukopenia: SSZ vs MTX, On-treatment

Source	cHR (95% CI)
CCAE	2.11 (1.29-3.45)
MDCR	
Optum	1.26 (0.78-2.05)
Amb_EMR	1.05 (0.51-2.16)
THIN	
GERMANY	
SIDIAP	
Summary (I2 = 0.39)	1.43 (0.96-2.15)



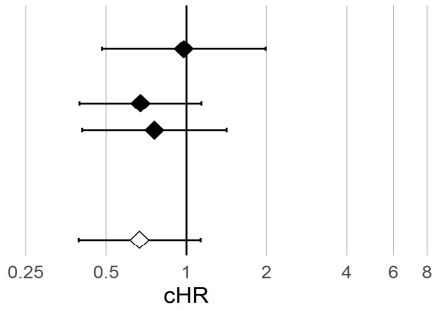
Pancytopenia: SSZ vs MTX, On-treatment

Source	cHR (95% CI)
CCAE	4.63 (1.66-12.91)
MDCR	
Optum	1.27 (0.61-2.62)
Amb_EMR	
THIN	
GERMANY	
SIDIAP	
Summary (I2 = 0.77)	



Leukopenia: LEF vs MTX, On-treatment

Source	cHR (95% CI)
CCAE	0.98 (0.48-1.98)
MDCR	
Optum	0.67 (0.40-1.14)
Amb_EMR	0.76 (0.41-1.42)
THIN	
GERMANY	
SIDIAP	
Summary (I2 = 0)	0.67 (0.39-1.13)



Pancytopenia: LEF vs MTX, On-treatment

Source	cHR (95% CI)
CCAE	0.92 (0.19-4.60)
MDCR	
Optum	0.53 (0.23-1.21)
Amb_EMR	0.51 (0.10-2.45)
THIN	
GERMANY	
SIDIAP	
Summary (I2 = 0)	0.50 (0.23-1.07)

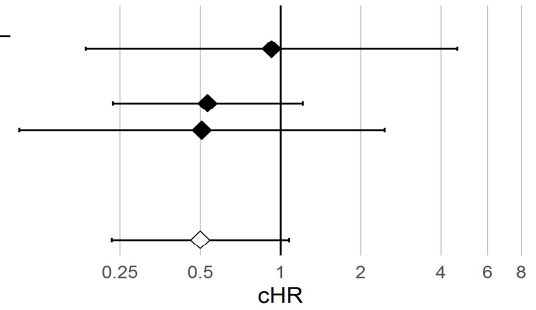


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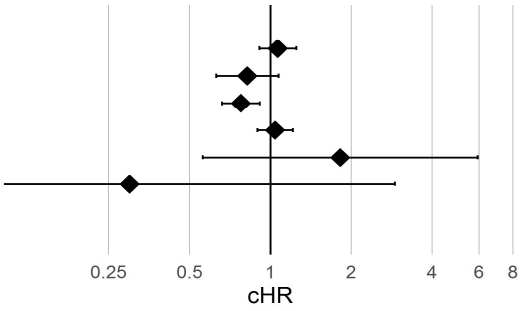
Figure 2. Calibrated hazard ratios (95% CI) vs MTX, ITT analysis

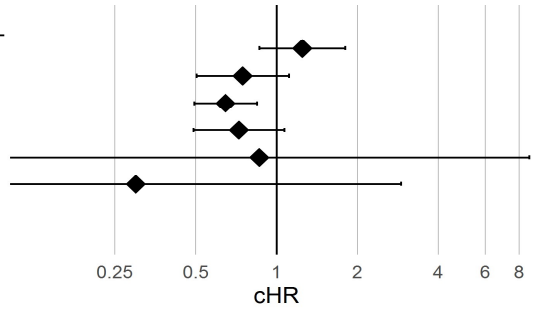
Leukopenia: HCQ vs MTX, ITT

Source	cHR (95% CI)
CCAE	1.06 (0.91-1.25)
MDCR	0.82 (0.63-1.07)
Optum	0.78 (0.66-0.91)
Amb_EMR	1.04 (0.89-1.21)
THIN	1.82 (0.56-5.92)
GERMANY	0.30 (0.03-2.90)
SIDIAP	
Summary (I2 = 0.69)	



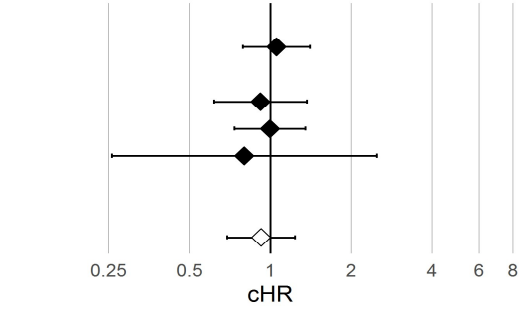
Pancytopenia: HCQ vs MTX, ITT

Source	cHR (95% CI)
CCAE	1.25 (0.86-1.80)
MDCR	0.75 (0.50-1.11)
Optum	0.64 (0.49-0.84)
Amb_EMR	0.72 (0.49-1.07)
THIN	0.86 (0.08-8.72)
GERMANY	0.30 (0.03-2.90)
SIDIAP	
Summary (I2 = 0.46)	



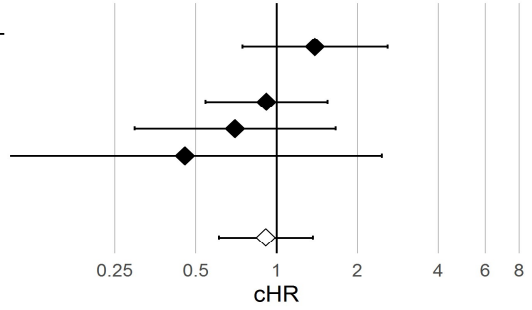
Leukopenia: SSZ vs MTX, ITT

Source	cHR (95% CI)
CCAE	1.05 (0.79-1.40)
MDCR	
Optum	0.92 (0.62-1.37)
Amb_EMR	1.00 (0.73-1.35)
THIN	0.80 (0.26-2.49)
GERMANY	
SIDIAP	
Summary (I2 = 0)	0.92 (0.69-1.24)



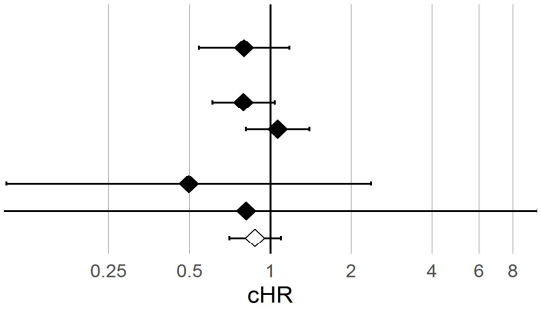
Pancytopenia: SSZ vs MTX, ITT

Source	cHR (95% CI)
CCAE	1.39 (0.75-2.59)
MDCR	
Optum	0.92 (0.54-1.55)
Amb_EMR	0.70 (0.30-1.66)
THIN	0.46 (0.08-2.46)
GERMANY	
SIDIAP	
Summary (I2 = 0)	0.91 (0.61-1.36)



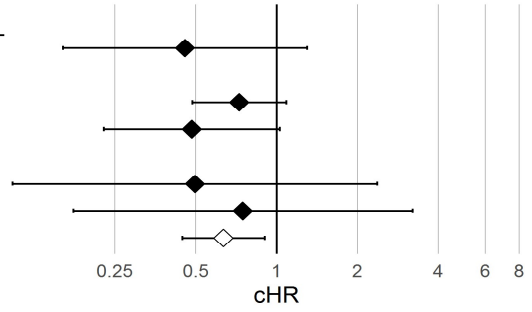
Leukopenia: LEF vs MTX, ITT

Source	cHR (95% CI)
CCAE	0.80 (0.54-1.18)
MDCR	
Optum	0.79 (0.61-1.04)
Amb_EMR	1.06 (0.81-1.40)
THIN	
GERMANY	0.50 (0.10-2.37)
SIDIAP	0.81 (0.07-9.88)
Summary (I2 = 0)	0.88 (0.70-1.09)



Pancytopenia: LEF vs MTX, ITT

Source	cHR (95% CI)
CCAE	0.46 (0.16-1.30)
MDCR	
Optum	0.73 (0.48-1.09)
Amb_EMR	0.48 (0.23-1.03)
THIN	
GERMANY	0.50 (0.10-2.37)
SIDIAP	0.75 (0.17-3.21)
Summary (I2 = 0)	0.63 (0.45-0.90)



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