JAKi and Balancing Risk: VTE, CVD, Infection, COVID

PANEL DISCUSSION

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Disclosures

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Consultant / Speaker: AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GSK, Janssen, Novartis, Pfizer, Sanofi Genzyme, Schipher Medicine, UCB

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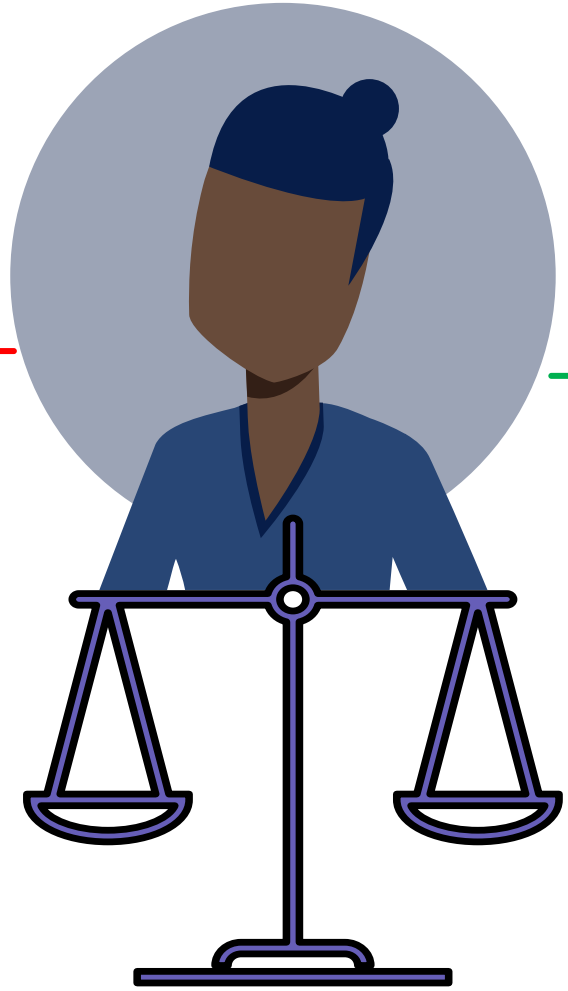
Consulting/Speaker: Alexion, AstraZeneca, Aurinia, Exagen Diagnostics, GSK, Kypha, Inc., Pfizer, Inc.

What are the Real Risks and Benefits for our Patients?

Social Determinants of Health



Healthcare costs

Infection

Malignancy

Cardiovascular disease

Thrombosis

Quality of Life

Joint Integrity

Psychological well-being

Work productivity

FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions

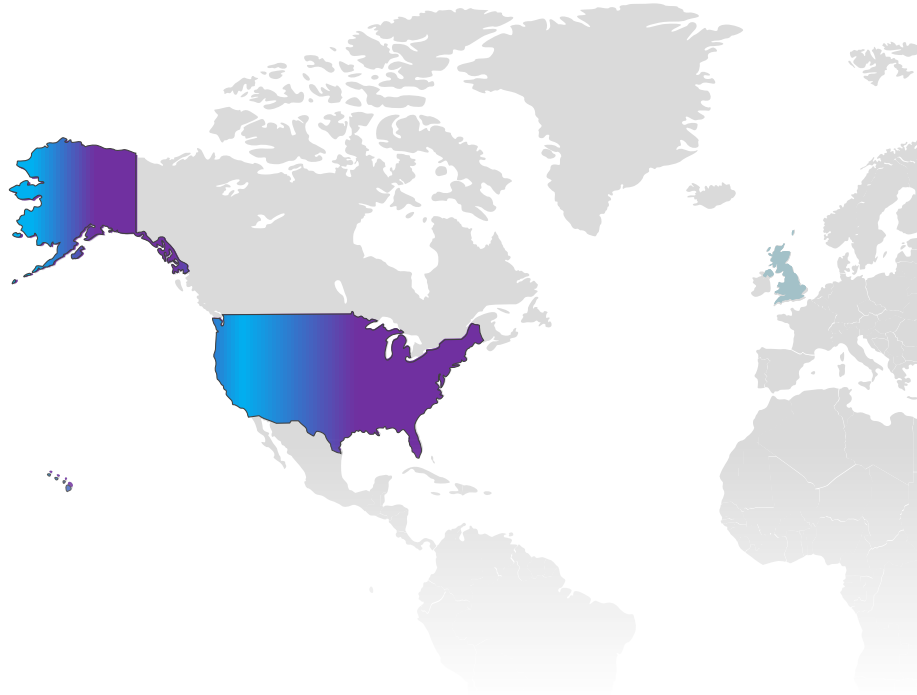
Approved uses also being limited to certain patients

https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death

VTE Incidence Rates and Risk Factors

- Data from 3 analyses of patients with RA found that the incidence rate of VTE ranged from 0.35 to 0.86 events per 100 PYs[1-3]

A population-based cohort study in US patients between 2001-2012, with a mean follow-up ranging from 0.6 to 1 year and 29,481 patients with RA who were initiating cs/b/nonbiologic DMARD therapy, reported incidence rates of VTE[1]* Defined as hospitalization for DVT or PE	The incidence rates per 100 PYs, using propensity scoring, were • 0.35 in MTX initiators • 0.44 in nonbiologic DMARD initiators • 0.48-0.55 in bDMARD initiators
A cohort study on US claims data between 2007 and 2017, with a follow-up of 164,477 PYs and 148,228 patients with RA required to be on cs/b/tsDMARD treatment, reported incidence rates of VTE[2†] Defined as the first hospitalized DVT or PE during follow-up	The age- and sex-standardized incidence rates per 100 PYs were • 0.58 in csDMARD users • 0.60 in first b/tsDMARD users • 0.86 in b/tsDMARD switchers
A cohort study in UK patients between 1994 and 2010, with a follow-up of 301,201 PYs and 51,762 patients with RA not on DMARD or on DMARD (including cs/b/nonbiologic DMARDs), reported the incidence rates of VTE[3,4‡] Defined as DVT or PE	The unadjusted incidence rates per 100 PYs were • 0.75 for patients not on DMARD • 0.79 for patients on DMARD



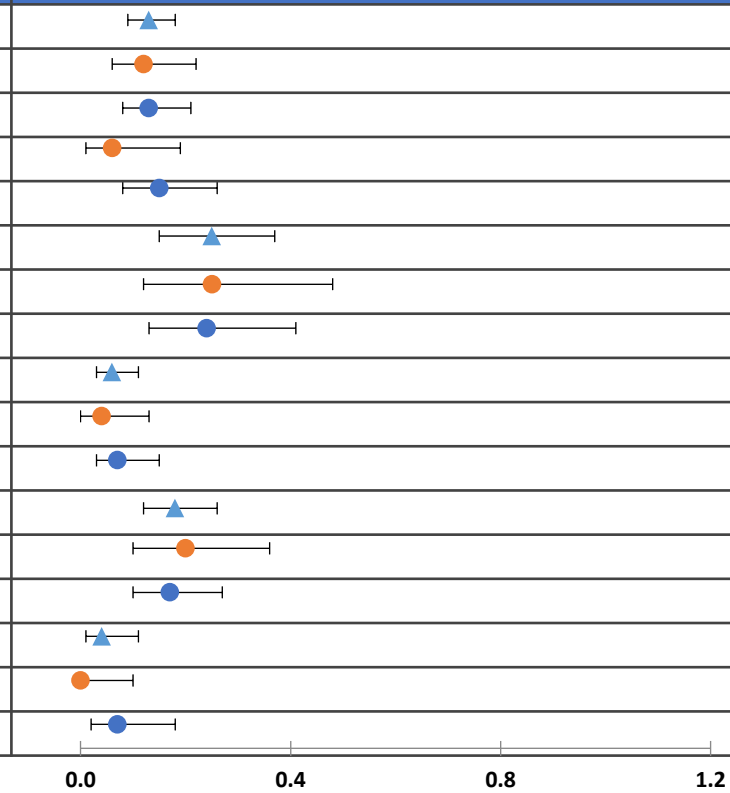
STUDY LIMITATIONS: Analyses based on real-world data are conducted under widely varying conditions including, but not limited to, study design, treatment exposure, and patient demographics. Any comparisons between studies cannot be made, and results from each analysis should be interpreted cautiously.

*Patient data were from 3 US health plans—WellPoint, United HealthCare, and Aetna. †Patient data were from the US claims database Optum Clinformatics Data Mart. Patients were required to have 1 year of continuous health plan enrollment before the index DMARD treatment. ‡Patient data were from the UK database The Health Improvement Network (THIN).

1. Kim SC, et al. *Am J Med.* 2015;128(5):539.e7-539.e17. 2. Liang H, et al. *RMD Open*. 2019;5(2). 3. Ogdie A, et al. *Eur Heart J.* 2018;39(39):3608-3614. 4. Supplement to: Ogdie A, et al. *Eur Heart J.* 2018;39(39):3608-3614. 5. Benjamin EJ, et al. *Circulation*. 2019;139(10):e56-e528.

Tofacitinib: Rates of PE Stratified by Baseline CV and VTE Risk Factors in RA Completed Trials Including LTE Data (All Tof Cohort) (Excluding ORAL Surveillance*)

			IR (95% CI)	n/N	IR (95% CI)	Drug exposure (PY)
		All tofacitinib doses		31/7964[c]	0.13 (0.09–0.18)	24107.1
		Average tofacitinib 5 mg BID		11/3969	0.12 (0.06–0.22)	9052.0
		Average tofacitinib 10 mg BID		20/3995[c]	0.13 (0.08–0.21)	15055.1
		Constant tofacitinib 5 mg BID		3/3292	0.06 (0.01–0.19)	4621.4
		Constant tofacitinib 10 mg BID		12/2876	0.15 (0.08–0.26)	7980.4
CV risk factor	**Yes**	All tofacitinib doses		22/3126[c]	0.25 (0.15–0.37)	8939.5
		Average tofacitinib 5 mg BID		9/1614	0.25 (0.12–0.48)	3538.3
		Average tofacitinib 10 mg BID		13/1512[c]	0.24 (0.13–0.41)	5401.2
	No	All tofacitinib doses		9/4838	0.06 (0.03–0.11)	15167.7
		Average tofacitinib 5 mg BID		2/2355	0.04 (0.0–0.13)	5513.8
		Average tofacitinib 10 mg BID		7/2483	0.07 (0.03–0.15)	9653.9
VTE risk factor	**Yes**	All tofacitinib doses		27/5257[c]	0.18 (0.12–0.26)	14979.1
		Average tofacitinib 5 mg BID		11/2633	0.20 (0.10–0.36)	5526.3
		Average tofacitinib 10 mg BID		16/2624[c]	0.17 (0.10–0.27)	9452.9
	No	All tofacitinib doses		4/2707	0.04 (0.01–0.11)	9128.0
		Average tofacitinib 5 mg BID		0/1336	0.00 (0.00–0.10)	3525.7
		Average tofacitinib 10 mg BID		4/1371	0.07 (0.02–0.18)	5602.2



Baseline CV risk factors were defined as patients aged ≥50 years and met any of the following criteria: current smoker, HDL <40 mg/dL, history of hypertension diagnosis, history of diabetes diagnosis, history of myocardial infarction or history of coronary heart disease diagnosis; **Baseline VTE risk factors** were defined as any patient meeting any of the following criteria at baseline: aged ≥60 years, current smoker, previous heart failure, previous VTE (DVT or PE), BMI ≥30 kg/m2, Day 1 use of oral contraceptives or hormone replacement therapy, Day 1 antidepressant use or Day 1 aspirin use. *Study A3921133. Data have not yet been source verified or subject to standard quality check procedures that would occur at the time of database lock and may therefore be subject to change; [c]One patient was not counted in the numerator of the IR calculations because the events occurred outside the defined risk period.

CV = cardiovascular. Mease PJ, et al. *Ann Rheum Dis*. 2020;79(11):1400–1413.

VTE Risk in RA (Real World)

Figure 67: Incidence Rates of VTE among RA Patients Reported in Published Observational Studies

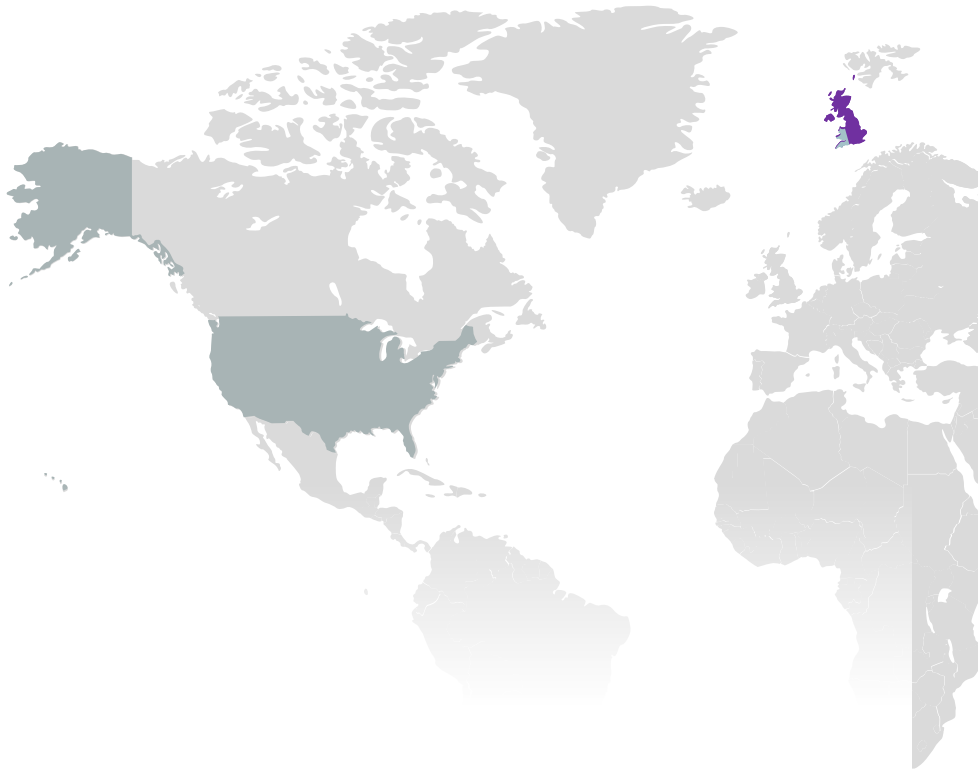
References	RA Cohort	Country	Data Source	N	Incidence Rate per 100 PYs (95% CI)
Ogdie 2017	DMARDS	UK	Medical records	31,336	0.79
Bacani 2012	RA	US	Medical records	464	
Eriksson 2017	RA	Sweden	National Register	43,490	
Kim 2013	DMARDS	US	Claims data	22,143	
Holmqvist 2012	RA (prevalent)	Sweden	National register	37,856	
Yusuf 2015	RA	US	Claims data	70,768	
Holmqvist 2012	RA (incident)	Sweden	National register	7904	
Davies 2011	nbDMARDs	UK	Registry (BSRBR)	3673	
Davies 2011	Anti-TNF	UK	Registry (BSRBR)	11,881	
Choi 2013	DMARD	UK	Medical records	9589	0.33

Abbreviations: BSRBR = British Society for Rheumatology Biologics Registers; DMARD = disease-modifying antirheumatic drug; nbDMARD = non-biologic disease-modifying antirheumatic drug; RA = rheumatoid arthritis; TNF = tumor necrosis factor; UK = United Kingdom; US = United States

MACE Incidence Rates and Risk Factors

- Data from 3 analyses of patients with RA found that the incidence rate of MACE ranged from 0.96 to 1.42 per 100 PYs[1-3]

A study using data from a US health insurance plan* from 2003 to 2012, with 32,007 PYs and 16,085 patients with RA on a variety of treatments (including cs/b/nonbiologic DMARDs), reported the incidence rate of MACE[1] Defined as nonfatal MI, CABG, coronary revascularization, or stroke	The unadjusted incidence rate per 100 PYs was • 1.42
A UK population-based longitudinal cohort study between 1994 and 2010, with a follow-up of 206,264 PYs and 41,752 patients with RA, on or not on a variety of treatments (cs/b/nonbiologic DMARDs), reported the incidence rate of MACE[2†] Defined as the first MI, CVA, or CV death	The unadjusted incidence rates per 100 PYs were • 1.11 for patients on DMARD • 1.35 for patients not on DMARD
A study using data from a Welsh data bank analyzing data between 1999 and 2013, with a follow-up of 57,005 PYs and 8650 patients with RA on a variety of treatments (including cs/b/nonbiologic DMARDs) reported the incidence rate of MACE[3,4‡] Defined as MI, CVA, or associated deaths	The unadjusted incidence rate per 100 PYs was • 0.96



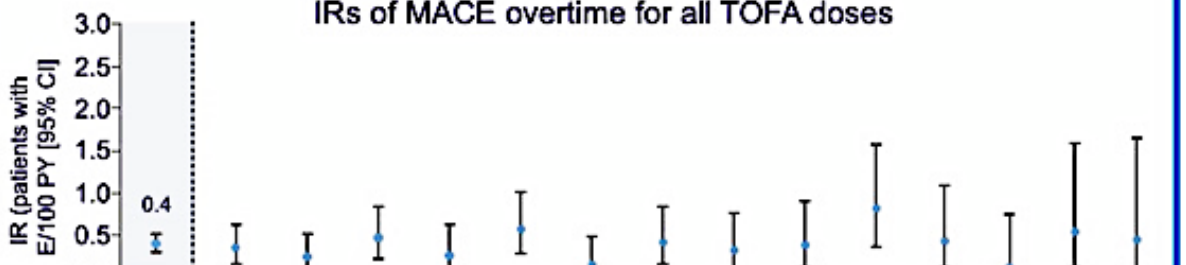
*Patient data were from the US United Healthcare database, and patients were identified with at least 2 visits coded with the ICD-9 for RA that are 7 days apart and at least 1 dispensing for a DMARD. †Patient data were from the UK database The Health Improvement Network (THIN). ‡Patient data were from the Welsh Secure Anonymised Information Linkage (SAIL) data bank, which includes GP data, hospital in- and outpatient records, and mortality data. RA was identified using GP records.

CABG=coronary artery bypass graft. CVA=cerebrovascular accident. CV=cardiovascular. ICD-9=International Classification of Diseases code, 9th Revision. GP=general practitioner.

1. Liao KP, et al. *Arthritis and Rheumatology*. 2015;67(8):2004-2010. 2. Ogdie A, et al. *Ann Rheum Dis*. 2015;74(2):326-332. 3. Cooksey R, et al. *Semin Arthritis Rheum*. 2018;48(3):367-373.
4. Supplement to: Cooksey R, et al. *Semin Arthritis Rheum*. 2018;48(3):367-373. 5. Benjamin EJ, et al. *Circulation*. 2019;139(10):e56-e528.

Tofacitinib: Integrated Safety Summary
Rates of MACE and Malignancy Over 9.5 Years of Follow-up

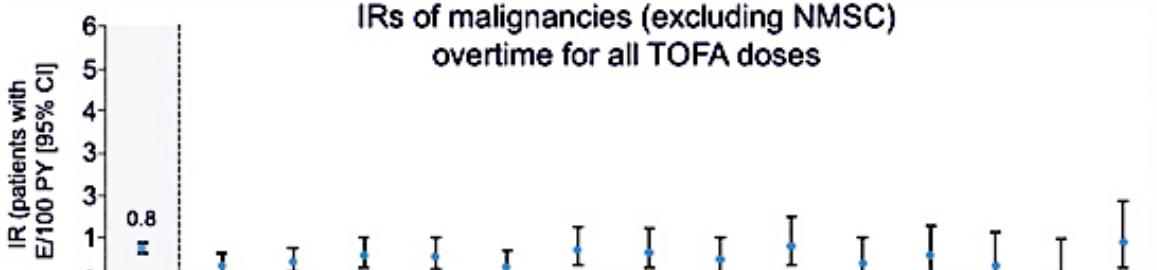
MACE (adjudicated)



	Overall	0–6	6–12	12–18	18–24	24–30	30–36	36–42	42–48	48–54	54–60	60–66	66–72	72–78	>78
Total patient exposure, n	6617	6617	6074	5502	4454	4126	3767	3530	3267	2820	2405	2063	1729	1310	894
Patients with MACE, n	85	11	7	11	6	11	3	7	5	5	9	4	1	3	2
Total PYE for event	22340.1	3141.5	2845.4	2311.6	2109.2	1924.5	1794.8	1683.9	1495.6	1286.0	1087.7	930.0	743.1	549.5	437.4

Adjudicated MACE was reported in 85 (1.3% patients (IR [95% CI] 0.4 [0.3 to 0.5])

Malignancy (excluding NMSC)



	Overall	0–6	6–12	12–18	18–24	24–30	30–36	36–42	42–48	48–54	54–60	60–66	66–72	72–78	>78
Total patient exposure, n	7061	7061	6243	5602	4558	4222	3854	3615	3372	2907	2511	2223	1837	1371	952
Patients with MACE, n	177	16	18	13	25	14	15	15	16	12	7	12	6	3	5
Total PYE for event	23416.0	3282.6	2902.2	2361.7	2160.3	1969.5	1837.6	1726.6	1545.5	1329.2	1156.6	1000.4	782.1	578.3	783.5

Malignancies (excluding NMSC) occurred in 177 (2.5% patients (IR [95% CI] of 0.8 [0.7 to 0.9])

Total exposure:
n=7061; 22,875 PY; median [range] exposure: 3.1 [0 to 9.6] years

The IRs for MACE and malignancies (excluding NMSC) were similar for both TOFA doses

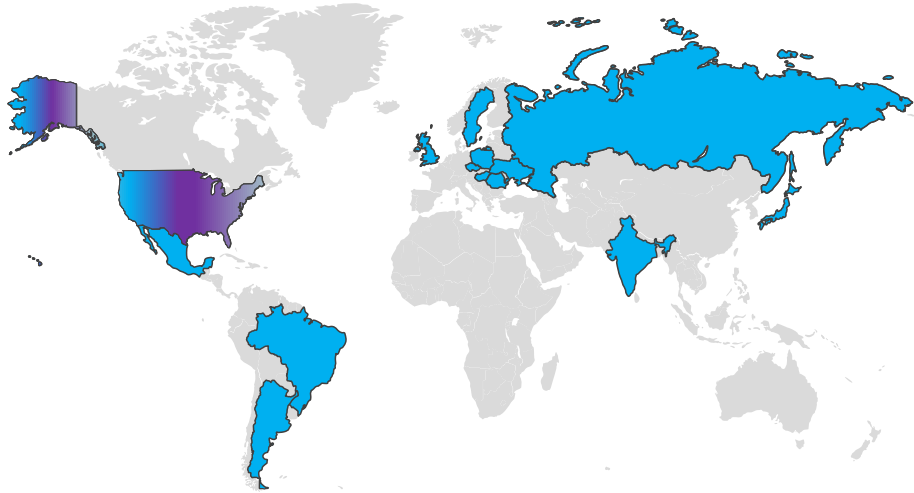
An analysis of IRs at 6-month intervals showed they were generally consistent over time

Cohen SB, et al. *RMD Open*. 2020;6(3):e001395. Open access.

Serious Infections Incidence Rates and Risk Factors

Data from 3 analyses of patients with RA found that the incidence rate of serious infections ranged from 1.14 to 2.69 per 100 PYs[1-3]

A prospective, coordinated analysis of 5 US and global RA registries* between 2000 and 2013 (n=58,389), for patients on a variety of treatments (including cs/b/nonbiologic DMARDs) reported the incidence rate of serious infections[1] Defined as an infection requiring hospitalization	The incidence rates, standardized by age and sex, per 100 PYs were • 1.14 for IORRA • 1.30 for CORRONA • 1.50 for CORRONA International • 1.56 for NOAR • 1.62 for SRR
A US-based longitudinal, observational, patient-reported data study from 2001 to 2016, with a follow-up of 81,499 PYs and 20,361 patients with RA on a variety of treatments (including bDMARDs), reported the incidence rate of serious infections[2†] Defined as an infection that required IV antibiotics (inpatient or outpatient), led to hospitalization, or was followed by death	The unadjusted incidence rate per 100 PYs was • 1.96
A US-based analysis focused on infection rates by csDMARDs/non-TNF inhibitor/TNF inhibitor use, with a follow-up of 27,552 PYs and 11,623 patients with RA from 2001 to 2016, reported the incidence rate of serious infections[3] Defined as requiring IV antibiotics or hospitalization or resulting in death	The crude incidence rates per 100 PYs were • 2.24 for csDMARDs • 2.33 for non-TNF inhibitor bDMARDs • 2.69 for TNF inhibitors

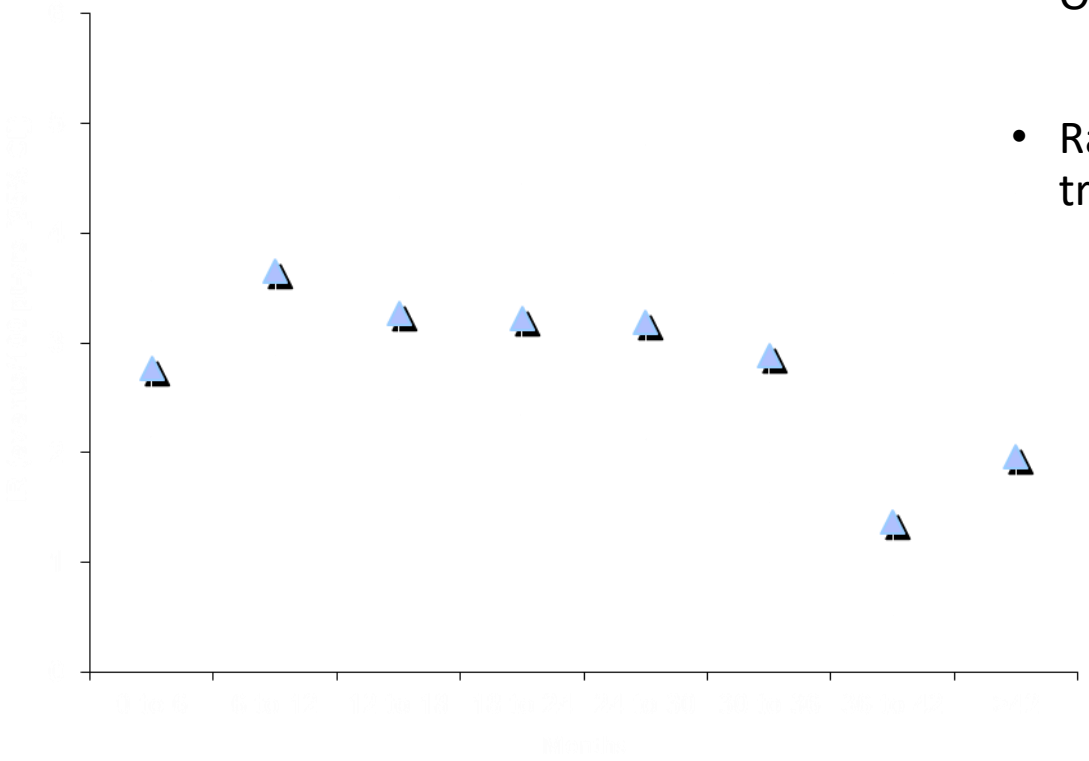


*CORRONA (US), SRR (Sweden), NOAR (UK), CORRONA International (Poland, Czech Republic, Hungary, Romania, Russia, Ukraine, Mexico, Brazil, Argentina, India), and IORRA (Japan). The definition of hospitalized infection was based on linked inpatient registry infection discharge codes in SRR and NOAR, patient-reported infection hospitalization in IORRA, and physician-reported infection hospitalizations in CORRONA and CORRONA International. †Patient data were from FORWARD—The National Databank for Rheumatic Diseases. FORWARD is ongoing and collects information from patients through questionnaires completed at 6-month intervals.

CORRONA=Consortium of Rheumatology Research of North America. SRR=Swedish Rheumatology Quality of Care Register. NOAR=Norfolk Arthritis Register. IORRA=Institute of Rheumatology, Rheumatoid Arthritis.

1. Yamanaka H, et al. *RMD Open*. 2017;3:e000498. 2. Mehta B, et al. *RMD Open*. 2019;5:e000935. 3. Ozen G, et al. *ACR Open Rheumatol*. 2019;1(7):424-432. 4. Arthritis Foundation Website. https://www.arthritis.org/health-wellness/about-arthritis/related-conditions/other-diseases/arthritis-and-infection-risk. Accessed August 19, 2020.

Incidence Rates of Serious Infections (SIs) by 6-Month Intervals

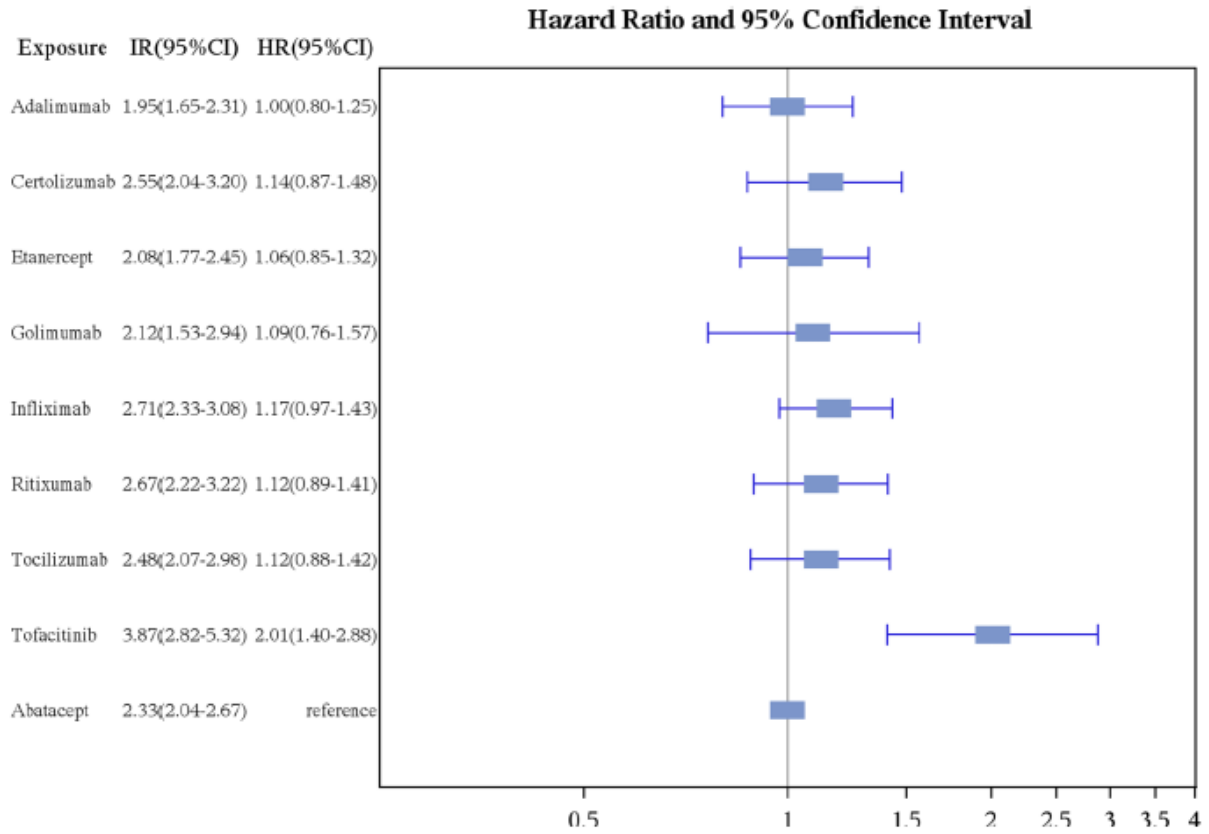


- Overall SI rate reported with tofacitinib:
  - 3.1/100pys
- Rates previously reported in RA clinical trial safety analyses
  - Adalimumab 3.9–5.1/100pys
  - Rituximab 3.9–4.3/100pys
  - Tocilizumab 3.8–5.1/100pys
  - Etanercept 3.8/100pys
  - Abatacept 2.0–3.1/100pys
  - Golimumab 5.09/100pys

Cohen S, Radominski SC, Gomez-Reino JJ, et al. *Arthritis Rheumatol*. 2014 Jul 21. [Epub ahead of print]. Slide prepared by CSF.

Real World HZ with Tofa and Biologics

Figure 1 Incidence rates and adjusted* HRs of herpes zoster among tofacitinib and biologic-treated patients with RA. *Adjusted for age, gender, glucocorticoid use, methotrexate, number of biologics used, prior hospitalised infection, prior hospitalisation for other reasons, prior outpatient infection (other than varicella) and zoster vaccination. CI, confidence interval; HR, hazard ratio; IR, incidence rate; RA, rheumatoid arthritis.



Curtis JC, et al. *ARD.* 2016.

JAKi and COVID Severity

Table 2 Frequencies and proportions of outcomes in the ordinal COVID-19 severity scale according to baseline use of biologic or targeted synthetic disease-modifying antirheumatic drug for patients with rheumatoid arthritis at the time of COVID-19 onset (N=2869)

COVID-19 severity scale	Overall N=2869 n (%)	Abatacept n=237 n (%)	Rituximab n=364 n (%)	IL-6 inhibitors n=317 n (%)	JAK inhibitors n=563 n (%)	TNF inhibitors n=1388 n (%)
Not hospitalised	2256 (78.6)	181 (76.4)	210 (57.7)	271 (85.5)	409 (72.6)	1185 (85.4)
Hospitalised without oxygenation	137 (4.8)	12 (5.1)	20 (5.5)	13 (4.1)	28 (5.0)	64 (4.6)
Hospitalised with any oxygen or ventilation	319 (11.1)	26 (11.0)	80 (22.0)	24 (7.6)	86 (15.3)	103 (7.4)
Death	157 (5.5)	18 (7.6)	54 (14.8)	9 (2.8)	40 (7.1)	36 (2.6)

IL-6, interleukin 6; JAK, Janus kinase; TNF, tumour necrosis factor.

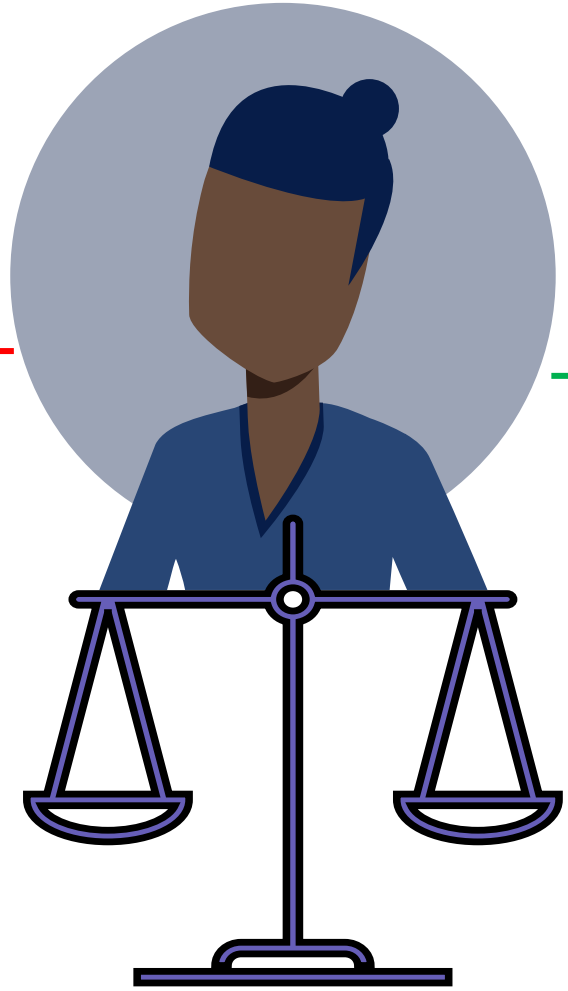
Table 4 Multivariable* OR of biologic or targeted synthetic disease-modifying antirheumatic drugs at each binary level of the COVID-19 severity scale (N=2869)

	Abatacept		Rituximab		IL-6 inhibitors		JAK inhibitors		
COVID-19 outcome	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	TNF inhibitors
Hospitalised	1.18 (0.76 to 1.82)	0.47	4.53 (3.32 to 6.18)	<0.01	0.84 (0.53 to 1.33)	0.45	2.40 (1.78 to 3.24)	<0.01	Ref
Hospitalised with oxygenation/ventilation or death	1.12 (0.70 to 1.81)	0.63	2.87 (2.03 to 4.06)	<0.01	0.72 (0.43 to 1.20)	0.20	1.55 (1.04 to 2.18)	0.01	Ref
Death	1.46 (0.72 to 2.89)	0.30	4.57 (3.32 to 9.01)	<0.01	1.13 (0.50 to 2.59)	0.77	2.04 (1.58 to 2.65)	<0.01	Ref
Mechanical ventilation (restricted to only hospitalised patients, n=613)	1.41 (0.94 to 2.10)	0.09	4.05 (3.08 to 5.33)	<0.01	0.75 (0.51 to 1.10)	0.14	2.03 (1.56 to 2.62)	<0.01	Ref
Mechanical ventilation or death	1.14 (0.78 to 1.66)	0.50	4.44 (3.39 to 5.82)	<0.01	0.74 (0.50 to 1.09)	0.12	2.02 (1.56 to 2.61)	<0.01	Ref

*Adjusted for age, sex, region, calendar time, obesity, smoking, concomitant csDMARD use, glucocorticoid use/dose, comorbidity count, hypertension/cardiovascular disease, interstitial lung disease, cancer and rheumatoid arthritis disease activity.
csDMARD, conventional synthetic disease-modifying antirheumatic drug; IL-6, interleukin 6; JAK, Janus kinase; Ref, reference; TNF, tumour necrosis factor.

What are the Real Risks and Benefits for our Patients?

Social Determinants of Health



Healthcare costs

Infection

Malignancy

Cardiovascular disease

Thrombosis

Quality of Life

Joint Integrity

Psychological well-being

Work productivity