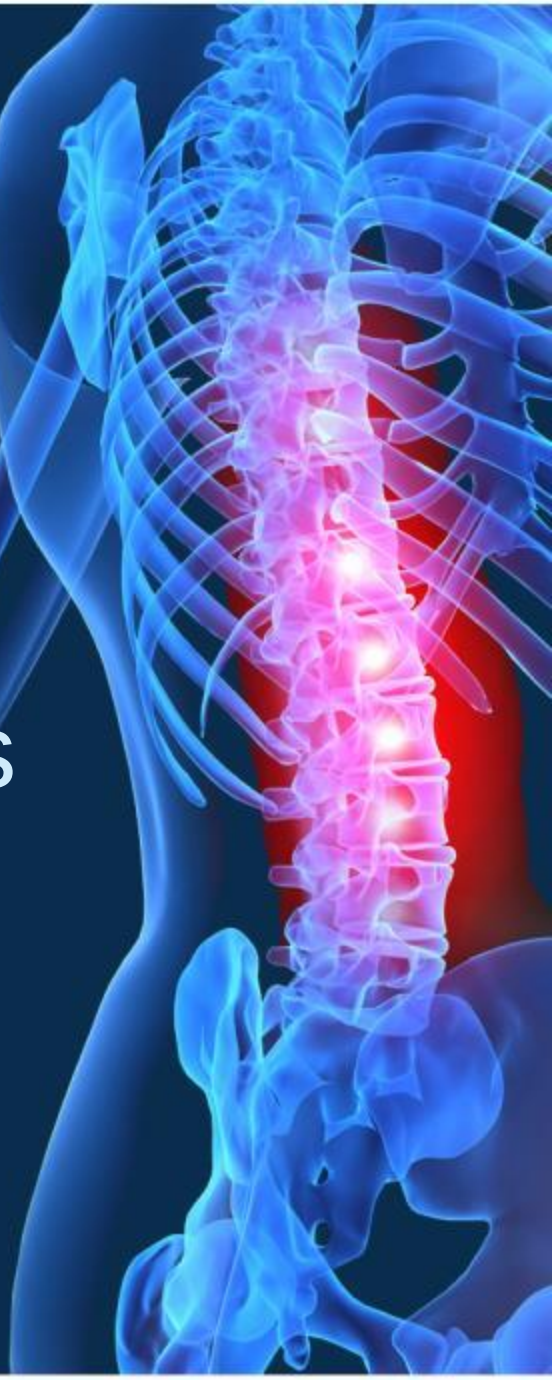
Annual Rheumatology & Therapeutics Review for Organizations & Societies



Serious Infections and Biologics

Learning Objectives

- Identify the spectrum of therapeutic agents currently approved for the treatment of inflammatory arthritis
- Distinguish the types of infections that are more common in patients using biological therapies
- Recognize and understand what vaccinations and other screening strategies should be employed in patients using biologic therapies

RA and Infection

	Incidence per 100 pt-yrs	Incidence per 100 pt-yrs.	
Infection type	**RA**	**Non-RA**	**RR (95% CI)**
Pneumonia	4.0	2.4	1.7 (1.5-1.9)
Skin	3.0	0.9	3.3 (2.7-4.1)
Sepsis	0.78	0.51	1.5 (1.1-2.1)
Septic joint	0.40	0.02	14.9 (6.1-73.7)
Intra-abdominal	0.22	0.08	2.8 (1.4-6.2)
Osteomyelitis	0.17	0.01	10.6 (3.4-126.8)

Doran et al. *Arthritis Rheum* 2002

Predictors of Serious Infection (Pre-Biologic Era)

- Retrospective cohort study of 609 RA patients
- Age/sex matched controls
- Followup = 13 years
- RRR infection = 1.53 RA
- Predictors of serious infection events (SIE) and infectious deaths are:
  - Disease severity/activity
  - Corticosteroid therapy
  - Comorbid diseases: CHF, CRF, IDDM, etc.
  - Skin infection/skin breakdown
  - Joint surgery
  - Certain DMARD therapy (CYP, CYA)
- Contributory role of other DMARDs [MTX, AZP, LEF] and biologics has NOT been established

Predictor	Hazard ratio	95% CI	*P*
Demographic variable			
Age,/10-year increment	1.49	1.33-1.67	<0.001
Male sex	1.28	0.96-1.72	0.099
Smoking	1.29	0.98-1.70	0.071
Body mass index	1.00	0.97-1.03	0.83
Comorbidities			
Alcoholism	2.00	1.27-3.16	0.003
Leukopenia	2.17	1.58-2.98	<0.001
Organic brain disease	2.94	2.08-4.16	<0.001
Diabetes mellitus	2.45	1.84-3.27	<0.001
Chronic lung disease	2.83	2.15-3.72	<0.001
Disease-related variables			
Extraarticular RA	3.22	2.17-4.77	<0.001
Rheumatoid factor	1.65	1.24-2.20	<0.001
Rheumatoid nodules	1.76	1.32-2.33	<0.001
Functional capacity	1.87	1.49-2.35	<0.001
ESR	1.83	1.23-2.18	<0.001
Medications			
Chemotherapy	5.02	2.44-10.3	<0.001
Methotrexate	0.91	0.57-1.45	0.69
Hydroxychloroquine	1.24	0.70-2.20	0.45
Sulfasalazine	1.08	0.81-1.43	0.61
Intramuscular gold	1.20	0.53-2.72	0.67
Oral gold	1.12	0.79-1.60	0.51
D-penicillamine	1.35	0.81-2.25	0.25
Leflunomide	2.22	0.88-5.64	0.093
Cyclophosphamide	6.14	3.12-11.8	<0.001
Cyclosporine	1.99	1.25-3.16	0.004
Etanercept	0.36	0.06-2.10	0.26
Corticosteroids	1.90	1.47-2.47	<0.001

Doran F. *Arthritis Rheum* 2002;46:2287-93

Prednisone and Hospitalized Pneumonia

	Unadjusted			Adjusted †		
Variable	**Hazard Ratio**	***P***	**95% CI**	**Hazard Ratio**	***P***	**95% CI**
Prednisone, all dosages	2.3	<0.001	1.9-2.7	1.7	<0.001	1.5-2.1
No prednisone	1.0			1.0		
Prednisone≤5 mg/day	1.7	<0.001	1.4-2.1	1.4	<0.001	1.1-1.6
Prednisone>5-10 mg/day	2.9	<0.001	2.3-2.7	2.1	<0.001	1.7-2.7
Prednisone >10mg/day	3.1	<0.001	2.2-4.3	2.3	<0.001	1.6-3.2
Methotrexate	1.0	0.951	0.9-1.2	1.0	0.884	0.8-1.2
Hydroxychloroquine	0.8	0.011	0.6-0.9	0.9	0.331	0.7-1.1
Leflunomide	1.3	0.003	1.1-1.6	1.3	0.036	1.0-1.5
Sulfasalazine	0.6	0.027	0.4-1.0	0.7	0.053	0.4-1.0
Infliximab	1.5	<0.001	1.3-1.7	1.2	0.182	0.9-1.4
Etanercept	0.7	0.013	0.5-0.8	0.8	0.051	0.6-1.0
Adalimumab	1.4	0.257	0.8-2.3	1.1	0.816	0.6-1.8

*95% CI – 95% confidence interval (see Table 1 for other definitions).
† Adjusted for age, sex,and for lagged variables of HAQ, pulmonary disease, diabetes, myocardial infarction, number of DMARDs or biologic agents, RA duration, smoking ever, education categories, safety registry membership, and prednisone usage (for nonprednisone variables).
Wolfe F, et al. *Arthritis Rheum* 54:628-34, 2006

Role of Steroid in Infection

- 1989 Meta-analysis 71 RCTs:
  - Cumulative prednisone doses >700 mg or daily dose 10mg/d
  - 60% higher risk for infectious complications in chronic disease
- Case control analysis: 16207 RA patients from Quebec, CA
  - 1947 SIE hospitalizations
  - cumulative doses of steroids in last 2-3 years increase risk of SIE
  - 5 mg/d prednisolone X 3 months: 30% increase SIE
  - X 6 months: 46% increase SIE
  - X 3 years: 100% increase SIE (equivalent to 30 mg/day for 1 month)
- BAD NEWS: 30-40% of RA patients are on chronic steroids
- GOOD NEWS: Risk for infection is reduced by 50% if steroids stopped X 6 months

Stuck AE. *Rev Infect Dis*. 1989 Nov-Dec;11(6):954-63.
Dixon WG. *Ann Rheum Dis*. 2012; 71(7):1128-33

Non-Biologic DMARDs

- Numerous cohort studies evaluating MTX
  - Little to no increased risk appreciated

Drug	RR (95% CI)
Cyclophosphamide	3.26 (2.28-4.67)
Glucocorticoids	2.56 (2.29-2.85)
Azathioprine	1.52 (1.18-1.97)
Methotrexate	1.10 (0.98-1.23)
Anti-malarials	1.06 (0.94-1.19)
Other DMARDS	0.92 (0.80-1.05)

Bernatsky S. et al. *Rheumatology* 2007;46:1157-60

Biologics in Rheumatoid Arthritis

Agent	Biologic Target	Construct
Infliximab	TNFα	Chimeric MAb
Etanercept	TNFαβ	IgG-p75 receptor
Adalimumab	TNFα	Human MAb
Goliumumab	TNFα	Human MAb
Certolizumab	TNFα	Peg-Fab’
Abatacept	T-cell costim	IgG-CTLA4 fusion
Rituximab	B-cells	Chimeric MAb
Anakinra	IL-1	IL-1 Recpt antag
Tocilizumab	IL-6	Anti-IL6 Recept MAb

* Tofacitinib is NOT a Bioilogic

Evaluating Infection Risk With Biologics

- Shortcomings of clinical trials:
  - publication bias
  - underpowered to demonstrate an increased risk
  - patients with history of infection or comorbidities excluded
  - Background DMARD/steroid different in different trials
  - Duration of follow-up short

- Shortcomings of Observational studies:
  - Channeling bias
  - Time bias (patients who do well remain in the study)
  - Recall bias (over-reliance of subject reporting)

Biologics May Give a 2x ↑ Serious Infections

Summary from Product Labels

	PI #s	Biologic SIE	Placebo SIE
Anakinra	3204	2%	1%
Adalimumab	2869	2%	1%
Etanercept	1637	1%	1%
Infliximab	1432	5.3%	3.4%
Golimumab	1526	1.9%	2.2%
Certolizumab	3476	3%	1%
Abatacept	1834	3%	1.9%
Rituximab	2578	2%	1%
Tocilizumab	4087	3.6 / 100py	1.5 / 100py
Tofacitinb	4800	3.2 / 100py	1.5 / 100py

“Real-World” Data: Serious Bacterial Infections

Table 3 The Biologic Era: Rates and RRs of Serious Infections in Patients with RA Using Anti-TNF Therapy From European and North American Observational Cohort Studies

Country, Year	Crude Incidence per 100 Patient-Years Anti-TNF Treated	Crude Incidence per 100 Patient-Years Nonbiologic Comparator	Adjusted Rr[a] (95% CI)
Germany,[37] 2005	6.4, ETN 6.2, INF	2.3	2.2 (0.9-5.4) ETN 2.1 (0.8-5.5) INF
United Kingdom,[34] 2007	5.5	3.9	1.3 (0.9-1.8)[c] 4.6 (1.8-11.9)[b]
United States,[8] 2007	2.9[d]	1.4[d]	4.2 (2.0-8.8)[d] 1.9 (1.3-2.8)
Sweden,[32] 2007	4.7	NR	1.4 (1.2-1.7)[e]
United States,[7] 2011	4.9	3.8	1.3 (0.8-2.1)
United States,[35] 2011	8.2	7.8	1.05 (0.9-1.2)
Germany,[10] 2011	4.8	2.3	1.8 (1.2-2.7)[f]
Japan,[91] 2011	6.4	2.6	2.4 (1.1-5.05)[g]

Abbreviations: ETN, etancercept; INF, infliximab; NR, not reported.
[a] Relative rate using nonbiologic users as the referent.
[b] When restricted to the first 90 days of therapy, and adjusted for age, sex, disease duration, and severity, extra-articular RA, baseline steroid use, diabetes, chronic obstructive pulmonary disease, pulmonary disease, and smoking history.
[c] Adjusted relative rate when not restricted to the first 90 days of therapy.
[d] Analysis restricted to the first 6 months after initiation of anti-TNF therapy.
[e] Rate calculated at 1 year after starting treatment and adjusted for RA severity and comorbidities associated with infections.
f Adjustment for time-varying risk factors, treatment adaptations, and dropout.
[g] Rate up to 1 year after drug start.
Winthrop KL. *Rheum Dis Clin N Am* 2012

Table 2. Initiation of TNF-α Antagonists and Risk of Serious Infections[a]					
Exposures	**Events, No.**	**Person-Years, No.**	**Rate, per 100 Person-Years**	**Hazard Ratio (95% CI) for Propensity Score- Matched Cohorts**	**Adjusted Hazard Ratios (95% CI)[b]**
Rheumatoid arthritis Nonbiologic regimens	326	4192	7.78	1 [Reference]	1 [Reference]
TNF-α antagonists	497	6089	8.16	1.05 (0.91-1.21)	1.05 (0.91-1.21)
Baseline gluccorticoid use, prednisone equivalents None					1 [Reference]
>0<5 mg/d					1.32 (1.10-1.58)
5-10 mg/d					1.78 (1.47-2.15)
>10 mg/d					2.95 (2.41-3.61)
Inflammatory bowel disease Azathioprine or mercaptopurine	87	906	9.60	1 [Reference]	1 [Reference]
TNF-α antagonists (infliximab or adalimumab)	107	961	10.91	1.09 (0.82-1.40)	1.10 (0.83-1.46)
Baseline glucocorticoid use, prednisone equivalents None					1 [Reference]
>0<5 mg/d					1.09 (0.72-1.65)
5-10 mg/d					0.93 (0.60-1.46)
>10 mg/d					1.38 (0.96-1.95)
Psoriasis and spondyloarthropathies [c] Nonbiologic regimens	63	1172	5.37	1 [Reference]	1 [Reference]
TNF-α antagonists	92	1699	5.41	1.07 (0.77-1.48)	1.05 (0.76-1.45)
Baseline gluccorticoid use, prednisone equivalents None					1 [Reference]
>0<5 mg/d					1.15 (0.75-1.77)
5-10 mg/d					2.01 (1.08-3.73)
>10 mg/d					2.77 (1.44-5.32)

Abbreviation: TNF, tumor necrosis factor.

[a] Estimates were stratified by database and all 95% Cis were based on robust SEs.

[b] Propensity score-matched cohorts plus adjustment for baseline glucocorticoid use.

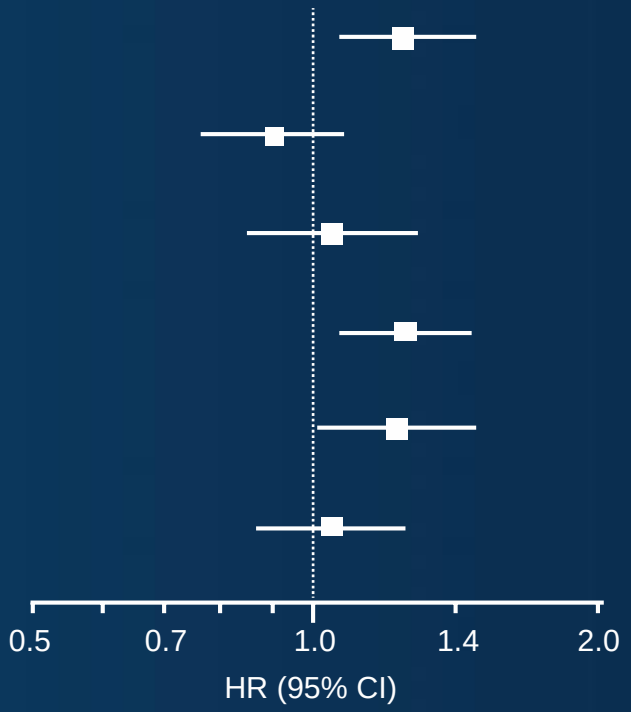
[c] Group includes patients with psoriasis, psoriatic arthritis, and ankylosing spondylitis.

Grijalva, C;*JAMA.* 2011;306(21):2331-2339

Differential Risk With Some TNFi

Figure 3. Incidence Rates with Hazard Ratios for Specific TNF-α Antagonists and Serious Infections Among Patients With Rheumatoid Arthritis

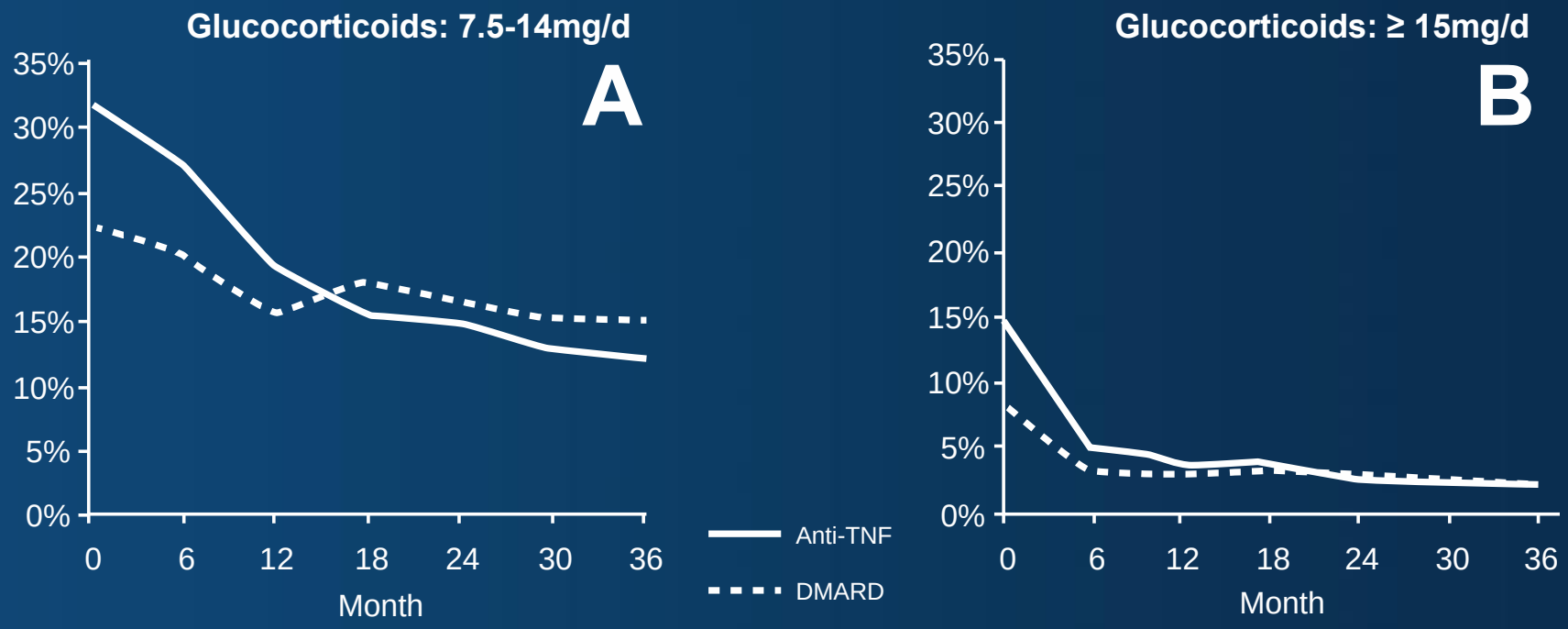
Treatment	No. of Events	Event Rate per 100 Person-Years	Hazard Ratio (95% CI)
Infliximab	420	10.3	1.25 (1.07-1.48)
Nonbiologic agent	234	8.8	1 [Reference]
Etanercept	264	6.8	0.91 (0.76-1.08)
Nonbiologic agent	233	7.6	1 [Reference]
Adalimumab	201	8.7	1.05 (0.85-1.30)
Nonbiologic agent	148	7.9	1 [Reference]
Infliximab	384	10.3	1.26 (1.07-1.47)
Etanercept	252	8.2	1 [Reference]
Infliximab	273	10.6	1.23 (1.02-1.48)
Adalimumab	183	8.9	1 [Reference]
Adalimumab	241	8.3	1.05 (0.87-1.25)
Etanercept	233	7.8	1 [Reference]



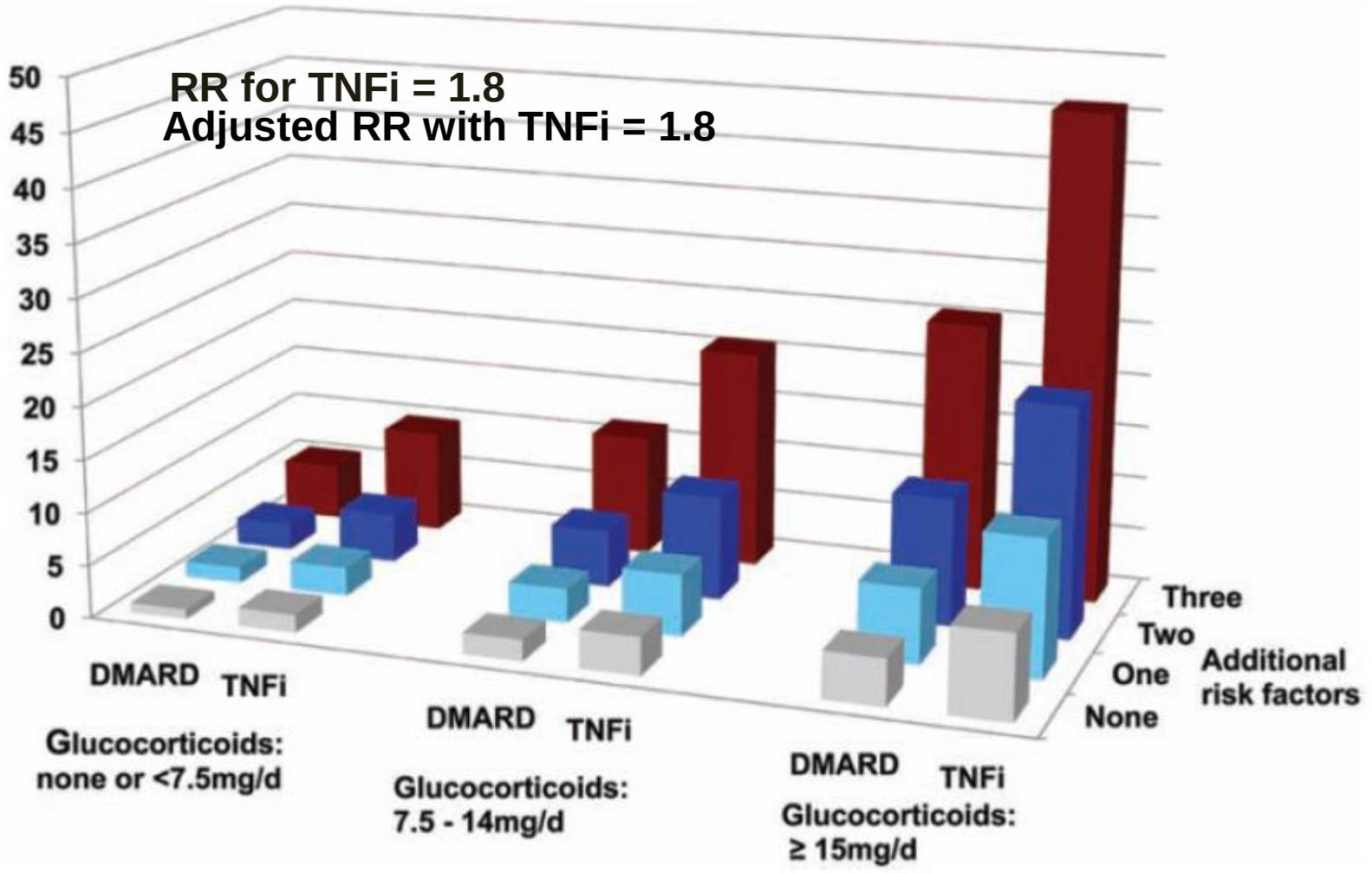
Each comparison required a separate propensity score matching iteration. TNF indicates tumor necrosis factor.

Grijalva C et al *JAMA* 2011

Prednisone Sparing Effect



Strangfeld A et al. ARD 2011



Strangfeld A et al. ARD Online; July 25, 2011

Infections in RA Patients > 65 yrs

- Seniors: more vulnerable
- Ontario admin claims data from 1992-2010
- 86,039 RA seniors - 20,575 infections

- Risk factors: comorbidities, rural, disease severity, prior infection
- DMARDs & TNFi increases OR 1.2 to 3.5 for infection

Infection	Event rate /1000 PY
Overall	46.36
Bacterial pneumonia	17.43
H. Zoster	8.54

Widdifield J, et al *Arthritis Care Res* 2013;65:353-61

Elderly Risk With TNFi

Age (years)	Serious Infection (per 100 pt-yrs)	Adj. HR*
<55	2.8	1.2 (0.8-1.6)
55-64	4.6	1.4 (1.1-1.9)
65-74	6.2	0.9 (0.7-1.2)
75+	8.3	1.5 (0.9-2.6)

*Adjusted for age, gender, COPD, DM, smoking, disease duration, DAS, HAW, steroids, MTX

Galloway JB et al. Rheumatology (Oxford).2011 Jan;50(1):124-31

Co-morbidities and Risk

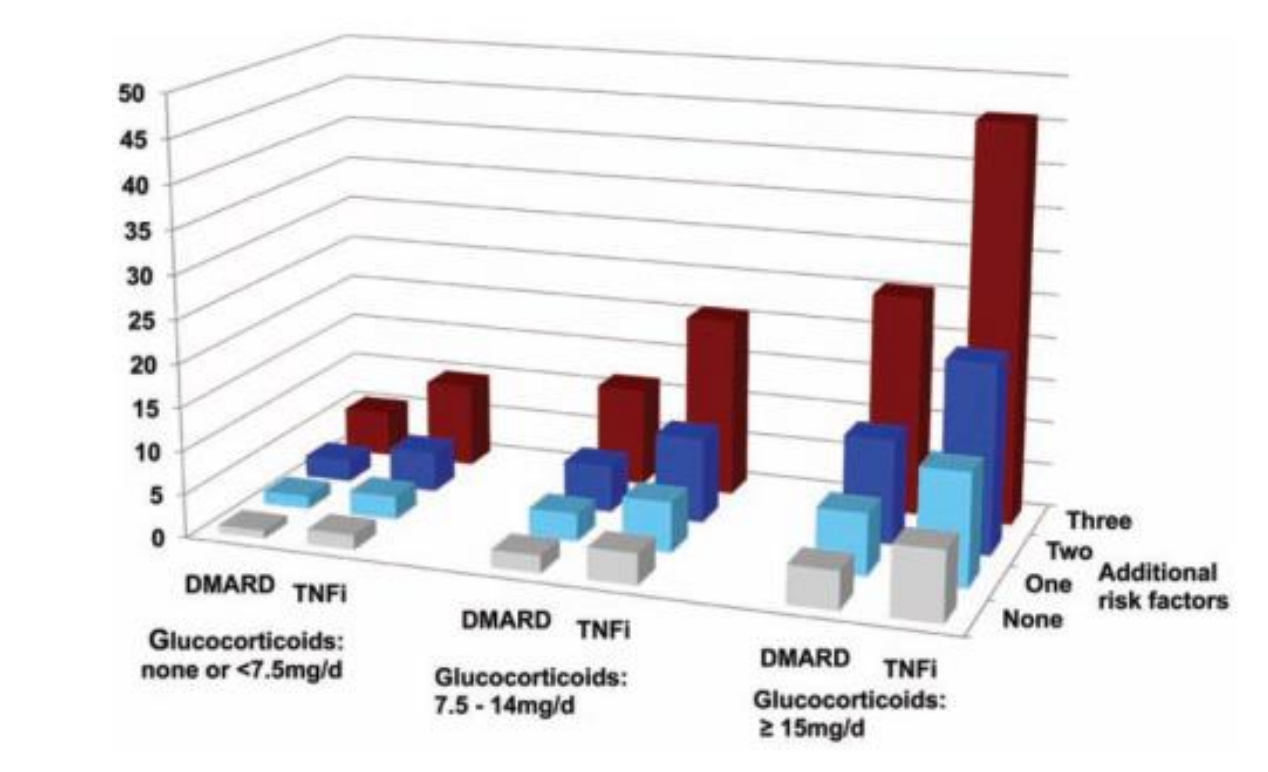
eTable 4. Rates of Serious Infections By Exposure and Baseline Characteristics. SABER (1998-2007)

Rheumatoid Arthritis

Subgroup	Exposure	Events	Person-years	Rate per 100 person-years (95% CI)
No hospitalizations for infection during baseline	TNF-antagonist MTX failure	375 228	5143.8 3527.5	7.3 (6.6 , 8.1) 6.5 (5.7 , 7.4)
Hospitalization(s) for infection during baseline	TNF-antagonist MTX failure	55 42	185.6 132.6	29.6 (22.8 , 38.6) 31.7 (23.4 , 42.9)
No baseline history of COPD	TNF-antagonist MTX failure	341 219	4704.3 3178.2	7.2 (6.5 , 8.1) 6.9 (6 , 7.9)
Baseline history of COPD	TNF-antagonist MTX failure	70 55	467.7 329.9	15 (11.8 , 18.9) 16.7 (12.8 , 21.7)
No baseline history of DM	TNF-antagonist MTX failure	316 221	4272.7 2931.3	7.4 (6.6 , 8.3) 7.5 (6.6 , 8.6)
Baseline history of DM	TNF-antagonist MTX failure	90 58	789.8 522.7	11.4 (9.3 , 14) 11. 1 (8.6 , 14.4)

Grijalva C et al *;* December 7, 2011, Vol 306, No. 21.

RABBIT Serious Infection Risk Calculator



- German Registry modeling of infection risk with development of validated calculator for serious infection risk based on patient factors and therapy

Zinck A, *Ann Rheum Dis*.2013 Jun 28 Epub

RABBIT Serious Infection Risk Calculator

RA patient #1
47 yr. old woman has no comorbidities, 2 prior DMARD failures, has 3 tender and 3 swollen joints, HAQ = 0.5, and takes MTX and prednisone 10 mg qd
SIE Risk = 1.4%
+TNF SIE Risk = 2.6%

RA patient #2
62 yr. old woman with COPD and prior pneumonia has failed 6 prior DMARDs/biologics, has 6 tender and 6 swollen joints and HAQ=1.2 while taking leflunomide and prednisone15 mg qd
SIE Risk = 28.4%
+TNF SIE Risk = 45.2%

*calculated from http://www.biologika-register.de

Cush JJ. *ACR Drug Safety Quarterly* 2013; 4 (4):1-3
Zinck A, *Ann Rheum Dis*.2013 Jun 28 Epub

SIE Risk in Those With Prior Biologic Therapy

Figure 1. Cumulative Incidence of Hospitalized Infection during One Year Follow-up

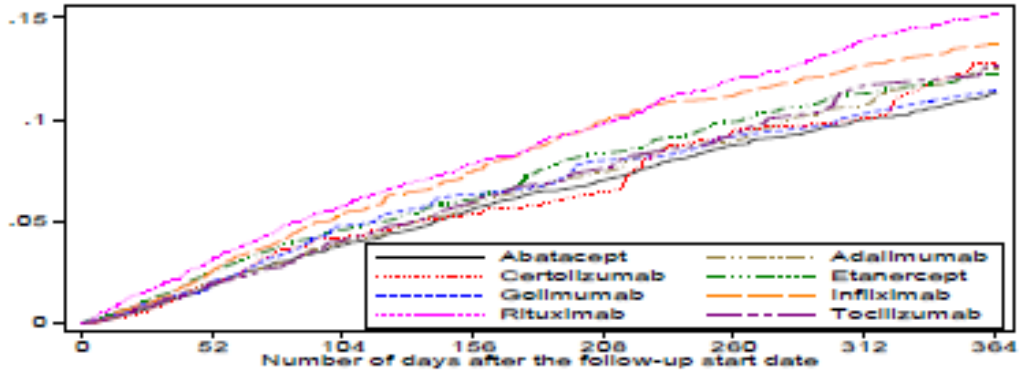


Table 2: Events, person years , crude incidence rate and adjusted hazard ratio * of hospitalized infection by biologic agent

Biologic agent	Events	Person years	Crude IR per 100 Pys (95% CI)	HR (95% CI)
Adalimumab	275	2020.9	13.6 (12.1-15.3)	1.07 (0.92-1.26)
Certolizumab	95	706.6	13.4 (11.0-16.4)	1.08 (0.87-1.35)
Etanercept	236	1621.0	14.6 (12.8-16.5)	**1.23 (1.04-1.44)**
Golimumab	77	572.3	13.4 (10.8-16.8)	1.15 (0.90-1.47)
Infliximab	327	2029.2	16.1 (14.5-18.0)	**1.38 (1.19-1.60)**
Rituximab	482	2741.7	17.6 (16.1-19.2)	**1.37 (1.21-1.56)**
Tocilizumab	112	816.7	13.7 (11.4-16.5)	1.10 (0.89-1.36)
Abatacept	632	5071.6	12.5 (11.5-13.5)	Ref

Adjusted for infection risk score decile, disability status, glucocorticoids use during baseline, methotrexate use during baseline, most recent biologic during baseline and Medicaid eligibility.

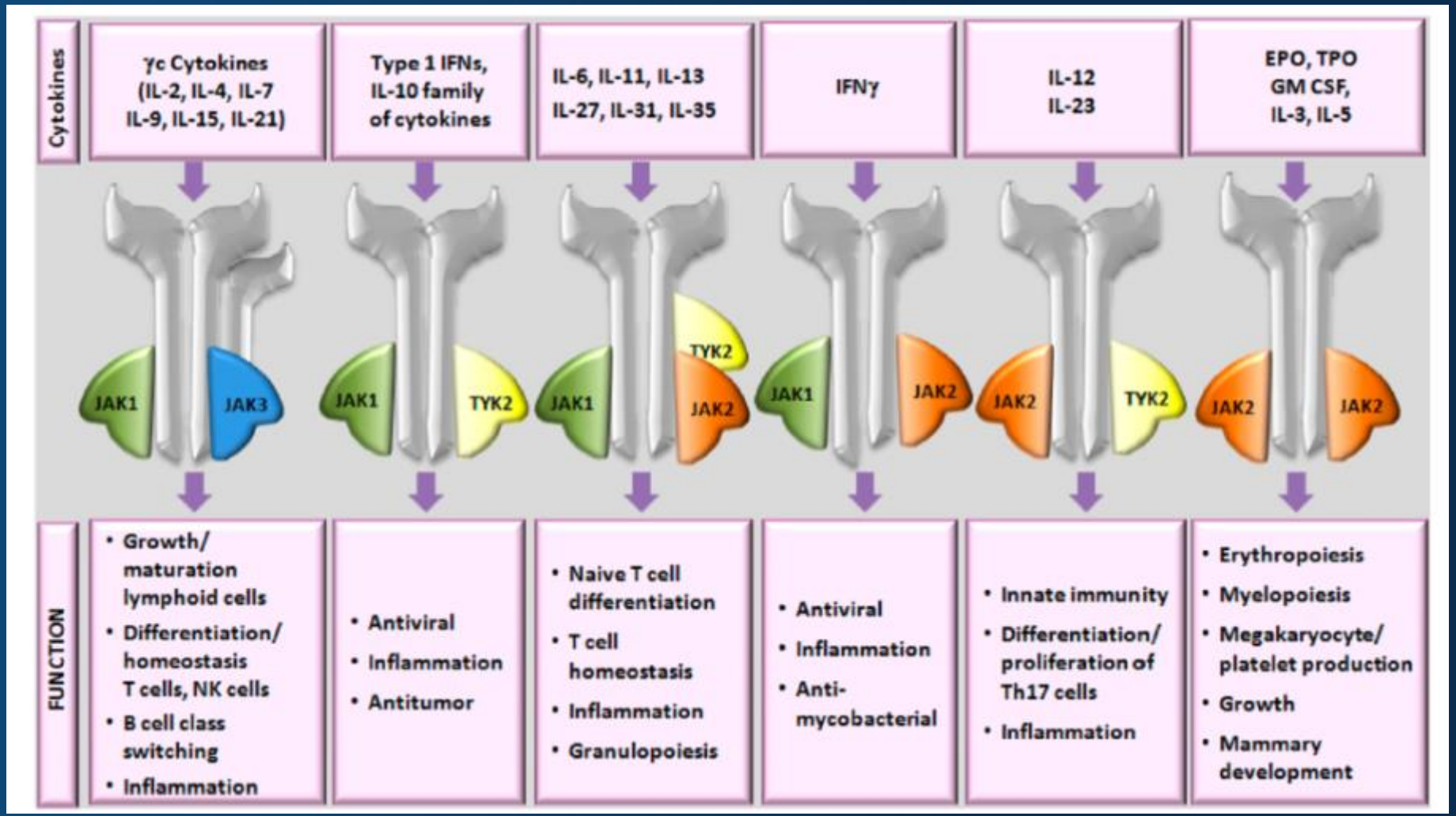
Yun H et al. *ACR abstract* San Diego 2013

TNF Inhibitors and Surgery

- Giles et al, 2006[1]
  - Retrospective cohort, patients with RA with orthopedic surgery (n = 91)
  - 10/91 with infection (7 anti-TNF vs 3 DMARD)
- den Broeder et al, 2007[2]
  - Retrospective cohort RA and orthopedic surgery (n = 768)
  - Perioperative anti-TNF *not* associated (OR = 1.5, [.43–5.2]) with infection
  - Wound dehiscence more common (OR = 11.2 [1.4–90])
- What do I do?
  - Stop one dosing interval prior to surgery and resume once wound healed
  - Recent BSR study supports[3]

BSR, British Society for Rheumatology; DMARD, disease-modifying antirheumatic drug.

Giles JT et al. *Arthritis Rheum*. 2006;55:333-337; 2. den Broeder AA et al. *J Rheumatol*. 2007;34:689-695.
3. Dixon WG et al. *Ann Rheum Dis*. 2007;66(suppl 2):118 [abstract OP0215].



Clark JD et al. *J Med Chem* 2014

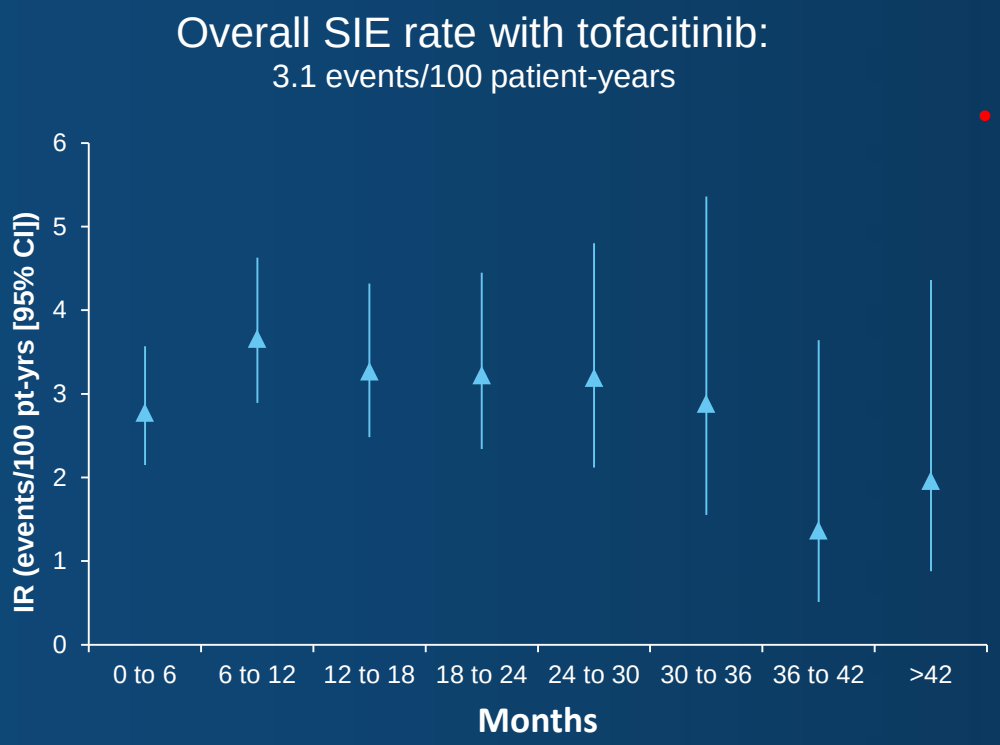
JAK Inhibitors for Rheumatology

Agent	Targeted JAKs	Indication	Stage of development
Tofacitinib	JAK1, JAK3	RA Psoriasis Ulcerative colitis JIA	FDA approved Phase 3 Phase 3 ongoing Phase 1
VX-509	JAK3	RA	Phase 2
R-348	JAK3	RA	Phase 1
INCB018424	JAK1, JAK2	Psoriasis (Topical Rx)	Phase 2
ASP015K	JAK 1, JAK3	RA Psoriasis	Phase 3 Phase 2
Baricitinib	JAK 1, JAK2	RA Psoriasis	Phase 2 Phase 2b
GLPG0634	JAK1, JAK2, TYK2	RA	Phase 2

Nature Reviews Rheumatology (9(3):173−82) 2013.

Results: Tofacitinib

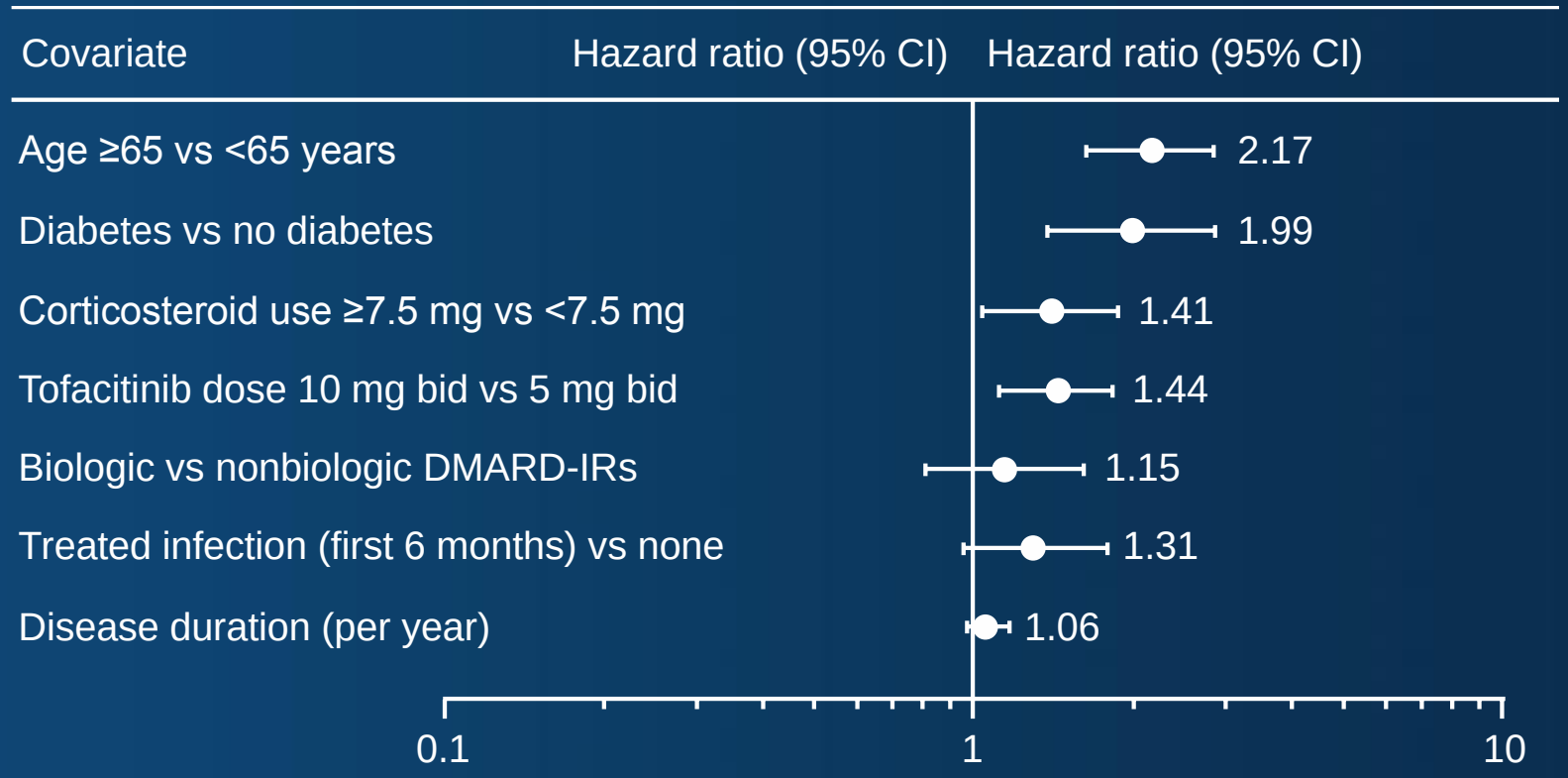
Incidence Rates of Serious Infections by 6-month Intervals



- Rates from clinical trials of biologics:
  - adalimumab 3.9–5.1 events/100 patient-years
  - rituximab 3.9–4.3 events/100 patient-years
  - tocilizumab 3.8–5.1 events/100 patient-years
  - etanercept 3.8 events/100 patient-years
  - abatacept 2.0–3.1 events/100 patient-years
  - golimumab 5.09 events/100 patient-years

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

Risk Factors for SIE with Tofacitinib



Cohen S, et al. *Arthritis Rheumatol*. 2014 Oct; 66(10): 2675–2684

Vaccines & Preventable Diseases

Live	Not-live
BCG Influenza (nasal) Mumps/Measles/Rubella Polio (oral) Rotavirus **Shingles** Smallpox Varicella Yellow Fever Typhoid (oral)	Anthrax Hepatitis A **Hepatitis B** **Influenza (IM)** *H. influenzae* **HPV** Japanese Encephalitis Meningococcal **Pneumococcal** Poliomyelitis (IM) Rabies **Tetanus/diptheria/pertussis** Typhoid (IM)

Pneumovax® (PPSV-23)

- Capsular polysaccharide vaccine
  - 23 serotypes
- Protective against invasive pneumococcal disease
  - Not clearly so for pneumonia
- Poorly immunogenic
  - Elderly, immunosuppresed
- Recommended
  - Immunocompetent adults > 65 years
  - All with chronic disease (>19 years)

MMWR. September 3, 2010 / 59(34);1102-1106; MMWR. October 12, 2012 / 61(40);816-819

PCV-13

- Conjugate vaccine
  - Covers 13 serotypes (12 from PPSV-23)
  - More immunogenic (in theory, but not evaluated yet in rheumatology patients)
  - Replaced PCV-7 in children
- How to use in adults?
  - Recommended in all patients > 65 yo
  - Recommended immunosuppressed patients of any age

Influenza

- Annual vaccine
  - Inactivated (IM) vaccine for rheumatology patients
  - High dose Flu-Zone®?
  - Quadrivalent
  - “Egg allergy” not a contraindication (unless history of anaphylaxis)
- 2014-2015 vaccine
  - A/California/7/2009(H1N1) A/Texas/50/201(H3N2) B/Massachusetts/2/2012 B/Brisbane/60/2008

HD Flu > 65 Years Old

- A total of 31,989 participants trivalent vaccine
  - High Dose (HD) versus Standard Dose (SD)
  - 228 (1.4%) Vs. 301 (1.9%) had laboratory-confirmed influenza
  - Relative efficacy, 24.2%; [95% CI (9.7 to 36.5)]
  - HD produced higher percentage of protective titers (HA titers ≥1:40)
- SAEs similar between groups
  - (8.3%) HD Vs. (9.0%) SD

Diaz Granados CA et al. NEJM 2014 Aug 14;371(7):635-45

Summary

- Best way to avoid serious infections:
  - Employ screening measures (when possible)
  - Rigorous Patient selection
  - Avoid or lower corticosteroid use
  - Maintain optimal disease control
  - Monitor signs and symptoms periodically
  - Vaccination where appropriate