

Safety Issues in Rheumatic Diseases: Minimizing Adverse Treatment Events and Related Comorbidities

Developed by the
Coalition of Rheumatology Educators (CORE™)





Learning Objectives

- Assess the safety issues associated with early aggressive and long-term management of RA
- Implement strategies to reduce frequent RA treatment adverse events, including infections and malignancies
- Summarize common comorbidities associated with uncontrolled disease in RA and SpA



Audience Response

The incidence rate of infections between patients treated with DMARD therapy and those treated with biologic therapy is similar.

1. Strongly agree
2. Agree
3. Somewhat agree
4. Somewhat disagree
5. Disagree
6. Strongly disagree

Serious Infections in Patients with RA Treated with TNF Inhibitors

- 8659 patients with RA treated with TNF inhibitors and 2170 patients with RA treated with DMARDs recruited to the BSRBR

Incidence of Infections among Patients with RA

	DMARD (n = 2170)	ETN (n = 3844)	INF (n = 2944)	ADA (n = 1871)	ALL TNF Inhibitors (n = 8659)
Person-years	532	917	723	451	2091
Number of infections	13	55	69	27	151
Rate of infections per 1000 person-years (95% CI)	24.4 (13.1-41.4)	60.0 (45.5-77.4)	95.4 (75.0-119.2)	59.9 (39.8-85.9)	72.2 (61.5-84.2)
Adjusted IRR (95% CI)*	Referent	4.1 (1.5-10.8)	5.6 (2.1-15.1)	3.9 (1.3-11.2)	4.6 (1.8-11.9)

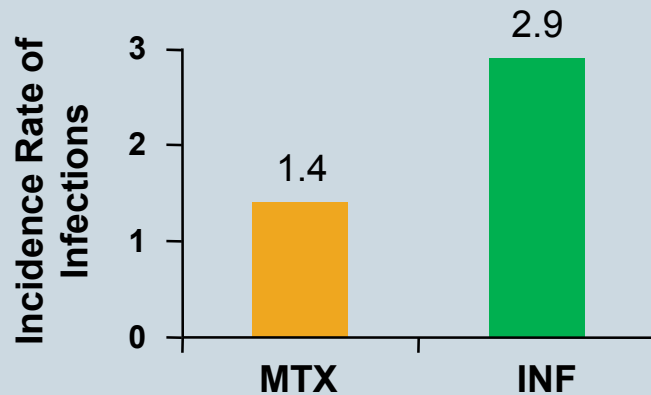
- Conclusion: risk of serious infection appears to be higher in TNF inhibitor-treated patients compared to DMARD-treated patients**

*Adjusted for age, sex, disease duration and severity, extraarticular RA, baseline steroid use, diabetes, chronic obstructive pulmonary disease, and smoking history. TNF = tumor necrosis factor; BSRBR = British Society for Rheumatology Biologics Register; ETN = etanercept; INF = infliximab; ADA = adalimumab; CI = confidence interval; IRR = incidence rate ratio.

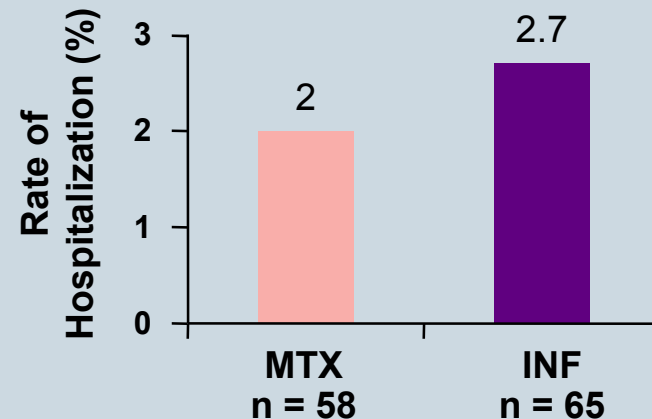
Serious Bacterial Infections Associated with RA and Risk of Hospitalization

- Patients treated with either TNF inhibitors (n = 2393; 3894 person-years) or MTX (n = 2933; 4846 person-years)
- Retrospective analysis of healthcare organization database cohort
- Female: 73%, median F/U: 17 months, and serious bacterial infections (ICD-9 codes x2) confirmed by trained nurse chart review and 2 infectious disease physicians

Incidence of Infections within 6 Months after Initiating TNF Inhibitors (per 100 Person-years)



Hospitalization with Confirmed Bacterial Infection

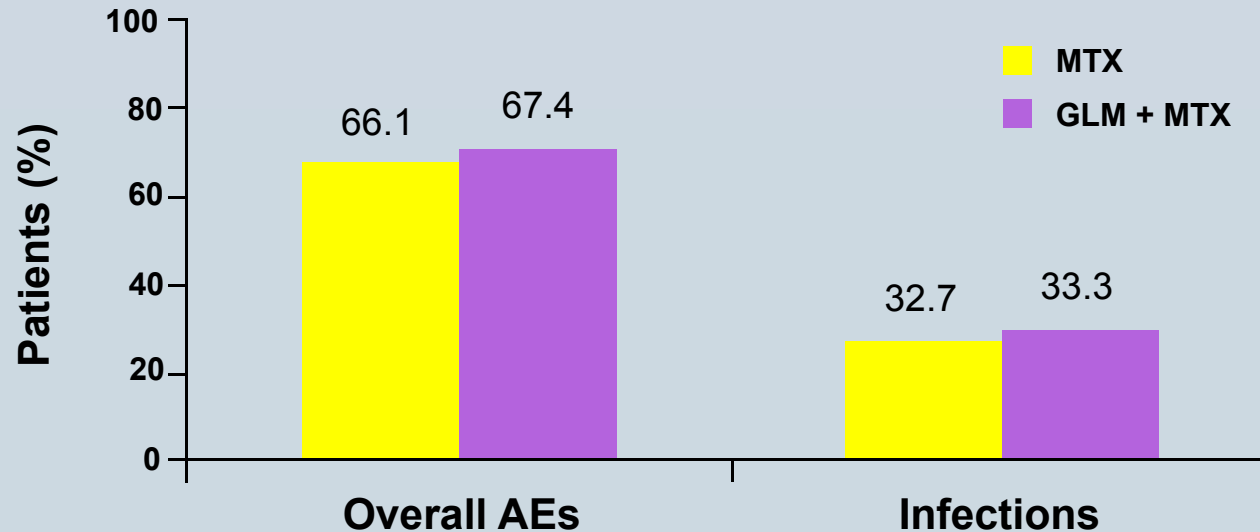


- **Conclusion: multivariable-adjusted risk of hospitalization was higher in patients treated with TNF inhibitors and rate of infections within 6 months of treatment initiation higher among this group**

Safety of GLM + MTX Therapy in RA

- 24-week, phase 3, randomized, double-blind, PBO-controlled study (N=643)
- Evaluated safety of GLM IV with or without MTX therapy vs. MTX monotherapy in MTX-inadequate responders with RA

Adverse Events at Week 16



- **Conclusion: Patients treated with either GLM + MTX or MTX monotherapy exhibited a similar rate of overall adverse events and infections**

Safety of CZP + MTX Therapy in Patients with RA

- Examined AEs developed by patients treated with CZP 200 mg + MTX, CZP 400 mg + MTX, or MTX + PBO
- Patients from RAPID 1 and RAPID 2 studies
- Most frequently reported infections were urinary tract infections, upper respiratory tract infections, and nasopharyngitis
- **Conclusion: incidence of AEs comparable among patients on CZP 200 mg + MTX and CZP 400 mg + MTX**

TEAEs (Safety Population)*

	PBO + MTX (n = 324)	CZP 200 mg + MTX (n = 640)	CZP 400 mg + MTX (n = 635)
Exposure (patient-years)	132	406.7	419.5
Serious AE	11.9	16.3	16.6
Infections	73.2	80.9	76.7
Serious infections	1.5	6	7.1
Malignancies	1.5	2	1.2
Cardiac disorders	5.3	4.7	4.8

*Number of new cases per 100 patient-years. CZP = certolizumab pegol; TEAEs = treatment-emergent adverse events. Mease PJ, et al. Presented at: 2008 EULAR Annual Meeting; June 11-14, 2008; Paris, France. Abstract FRI0120.

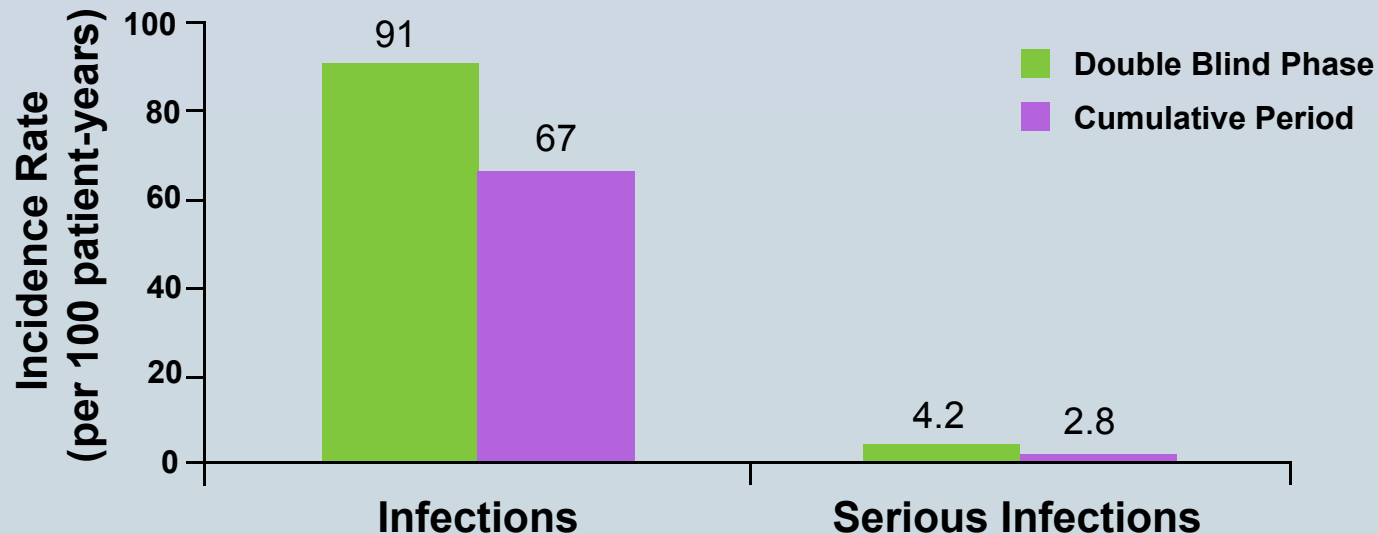
Serious Infections Among Patients with RA on Either RTX, ABA, or ANA

Source	Biologic	SIE Biologic (%)	SIE PBO (%)	ORs (95% CI)
Edwards et al, 2004	RTX	6/121 (4.9)	1/40 (2.5)	1.45 (0.56-3.73)
Emery et al, 2006		4/316 (1.2)	2/149 (1.3)	
Cohen et al, 2006		7/308 (2.3)	3/209 (1.4)	
Total		17/745 (2.3)	6/398 (1.5)	
Moreland et al, 2002	ABA	1/90 (1.11)	0/32 (0)	1.35 (0.78-2.32)
Kremer et al, 2005		1/220 (0.45)	2/119 (1.7)	
Genovese et al, 2005		6/258 (2.3)	3/133 (2.2)	
Kremer et al, 2006		13/433 (3.0)	5/219 (2.3)	
Weinblatt et al, 2006		28/959 (2.9)	8/482 (1.6)	
Total	49/1960 (2.5)	18/985 (1.8)		
Bresnihan et al, 1998	ANA	5/351 (1.42)	1/121 (0.82)	2.75 (0.90-8.35)
Cohen et al, 2002		0/345 (0)	0/74 (0)	
Cohen et al, 2004		2/250 (0.80)	2/251 (0.8)	
Schiff et al, 2004		23/1116 (2.0)	1/283 (0.3)	
Total		30/2062 (1.4)	4/729 (0.5)	

Long-Term Safety of ABA in Biologic-Naïve Patients with RA

- Patients from a 1-year, randomized, double-blind, PBO-controlled study (patients originally had inadequate response to MTX)
- Examined safety of ABA over 5 years in 219 patients with RA who entered OLE

Incidence Rates of Infections and Serious Infections



- **Conclusion: Patients receiving ABA had sustained ACR responses over the course of the 5-year OLE, with no increase in the incidence of AEs**

Safety Issues with Long-Term Use of RTX in Patients with RA

- Evaluated long-term safety of MTX + RTX in clinical trial patients (5964 patient-years)
 - 2579 patients with RA received multiple courses (C) of RTX; 1926, 1228, 794, and 282 patients received ≥ 2 , ≥ 3 , ≥ 4 , and ≥ 5 courses, respectively
- Withdrawals from AEs occurred in 138 patients (5%)
- Overall serious infection rate was 4.26 per 100 patient-years (95% CI: 3.77, 4.82)
- 1 case of PML was reported in a patient who also received cancer chemotherapy

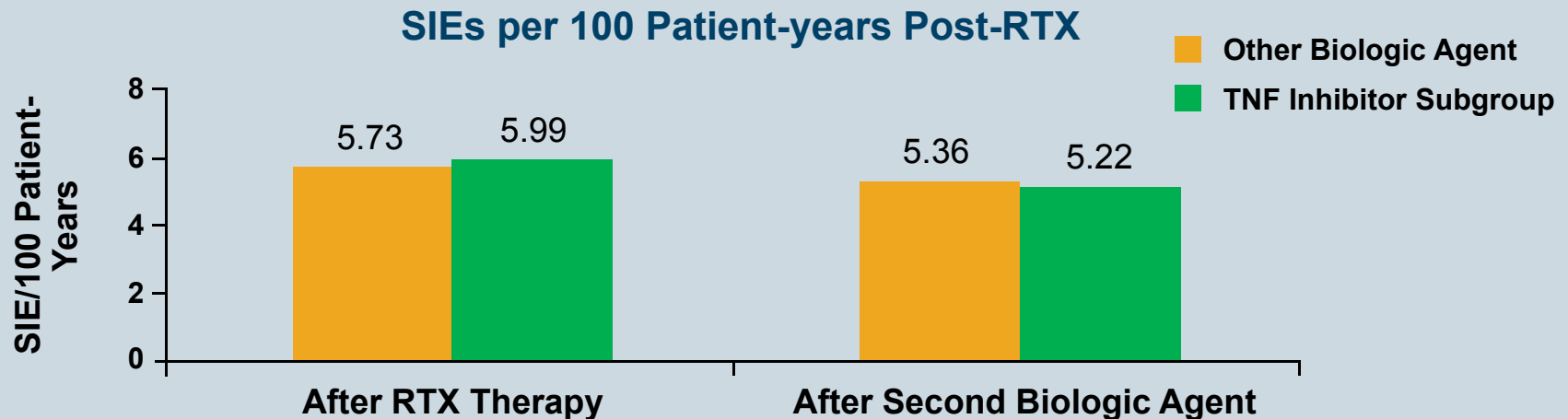
Rates of AEs per 100 Patient-years

	C1 (n=2579)	C2 (n=1926)	C3 (n=1228)	C4 (n=794)	C5 (n=282)
Total patient-years	2594	1877	900	409	119
Any AEs (95% CI)	379 (371-386)	313 (305-321)	319 (308-331)	329 (312-348)	330 (299-364)
Any SAEs (95% CI)	18.3 (16.7-20)	17.4 (15.6-19.4)	16.6 (14.1-19.4)	12 (9.1-15.9)	13.4 (8.2-21.9)
Infections (95% CI)	97 (93-100)	94 (90-99)	108 (102-115)	102 (93-113)	96 (80-116)
Serious infections (95% CI)	4.66 (3.90 – 5.57)	3.62 (2.86-4.60)	4.22 (3.07-5.80)	3.91 (2.40-6.38)	5.87 (2.80-12.30)

- **Conclusion: when given long-term, RTX is well tolerated in patients with RA**

Serious Infections in Patients Switched to a Second Biologic Agent Following RTX

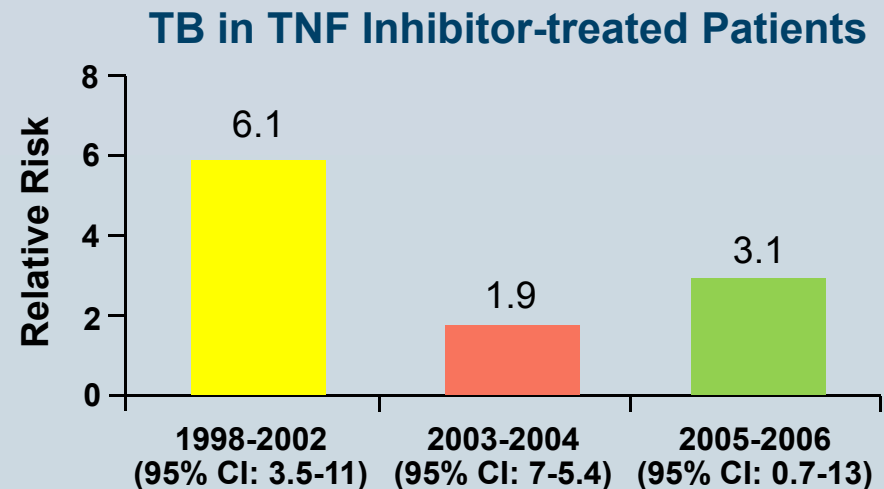
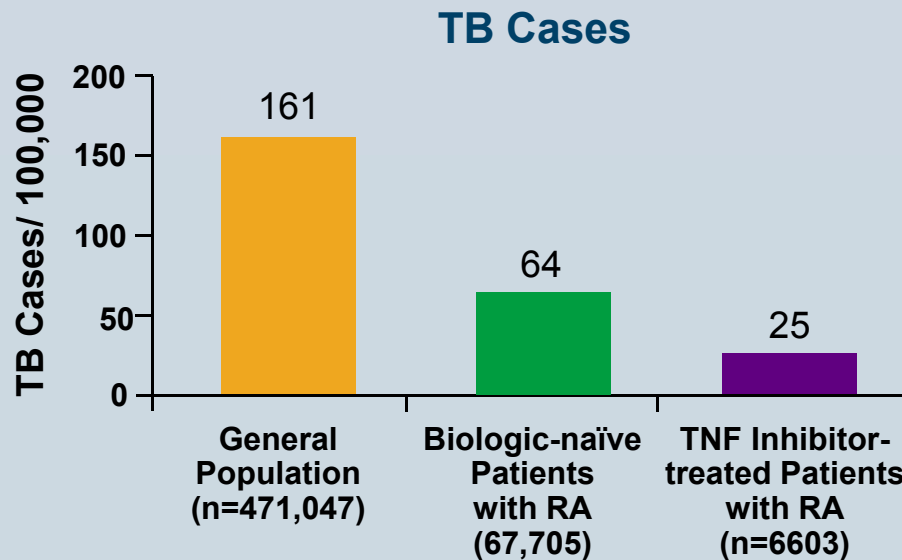
- Assessed rate of SIEs in patients with moderate-to-severe RA who received RTX and then switched to another biologic agent while peripheral B cells were depleted
- 216 patients subsequently treated with a biologic agent (178 patients received a TNF inhibitor, 31 patients received ABA, and 9 patients received ANA)
- About 35% of patients received a second biologic agent within 6 months of last RTX infusion
 - Number of SIEs after RTX if a biologic agent was started or if a TNF inhibitor was started was 13 vs 11, respectively; number of SIEs after a second biologic agent was started or after a TNF inhibitor was started was 12 vs 10, respectively
- Median time to SIE after initiating biologic therapy was 6 months



- **Conclusion: no significant increase in rate of SIEs when switching to a second biologic agent in patients who have received RTX**

Risk of TB in TNF Inhibitor-Treated Patients with RA

- Evaluated whether risk of TNF-inhibitor-associated TB is a time-limited issue
- Patients with RA from ARTIS registry and individuals from the general population register
- 3 cohorts created: patients with RA on TNF inhibitors, biologic-naïve patients with RA, and individuals from the general population



Conclusions:

- RA is a risk factor independent of TNF inhibitor use in patients with RA
- TB continues to be a risk for the group of patients with RA treated with TNF inhibitor therapy

Invasive Fungal Infections with TNF Inhibitor Therapy

- MEDLINE and PubMed database search from 1966-2007 (N = 281)
- Median time until onset of invasive fungal infection:
 - INF: 55 days
 - ETN: 144 days
- Median age of patient when developing invasive fungal infection was 58 years
- Histoplasmosis was the most prevalent invasive fungal infection (30%)
- Pneumonia was the most common pattern of infection (32%)
- 29 fatalities (32%) among the 90 cases for which outcome information was available of the total 281 cases

Fungal Infections Associated with TNF Inhibitor Therapy

Infectious Agents	INF	ETN	ADA
<i>Aspergillus</i> species (n=64)	48	14	2
Zygomycetes (n=4)	3	NC	1
<i>Candida</i> species (n=64)	54	9	1
<i>Cryptococcus</i> species (n=28)	17	10	1
<i>Blastomyces</i> species (n=2)	ND	ND	ND
<i>Coccidioides</i> species (n=29)	27	2	NC
<i>Histoplasma</i> species (n=84)	72	8	4
<i>Sporothrix</i> species (n=1)	1*	NC	NC
<i>Prototheca</i> species (n=1)	1	NC	NC
Tinea or pityriasis versicolor (n=6)	3	1	2
Total	226	44	11

*In this case etanercept was used as well, but symptoms worsened while the patient received INF. ND = no data available; NC = no cases identified.
Tsiodras S, et al. *Mayo Clin Proc.* 2008;83(2):181-194.

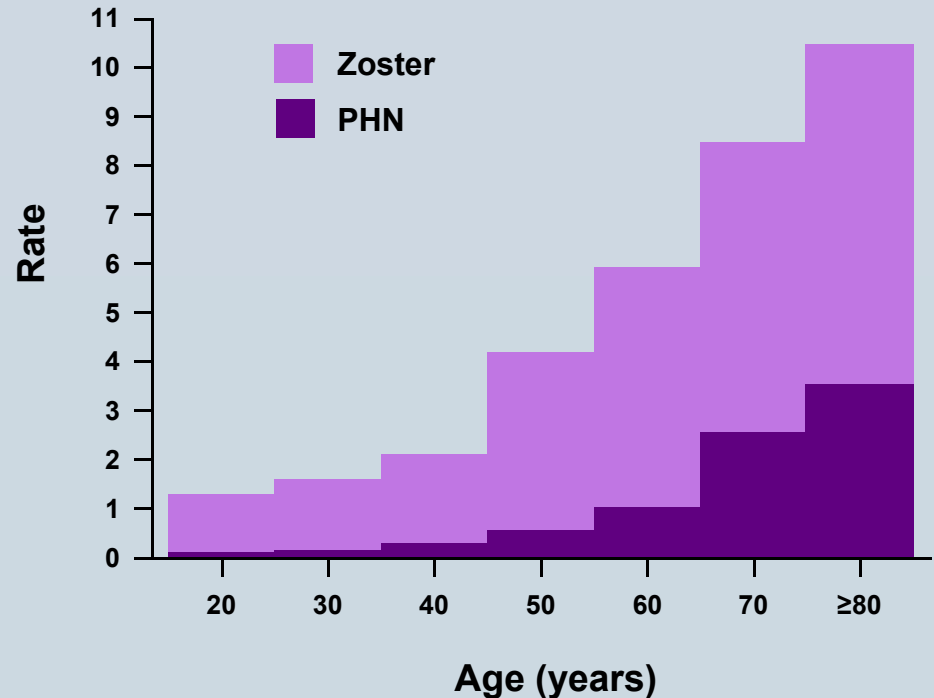
Vaccination in Patients with RA

- Study examined efficacy and safety of influenza vaccine in 112 patients (82 patients with RA; 30 healthy controls)¹
 - **Conclusion: patients with RA had lower responses to influenza vaccine compared to healthy controls**
- Vaccination use in patients on disease-modifying therapy
 - Influenza vaccine: humoral responses largely unaffected by prednisone, MTX, TNF inhibitors, ABA^{2,3}
 - Pneumococcal vaccine: TNF inhibitors do not affect patient response,² however RTX blunts patient response; best to vaccinate before RTX⁴
 - Overall, best to vaccinate before use of biologic therapy
 - Do not give live vaccines to patients with RA

CDC/ACIP Guidelines for Zoster Vaccine

- Do not use vaccine in immunocompromised patients with:
 - Recombination biologics (especially TNF inhibitors) or high-dose steroids
 - Active leukemia, lymphoma, malignant neoplasms affecting bone marrow
 - AIDS/HIV or evidence of cellular immunodeficiency
 - Stem cell transplantation, pregnancy, and acute illness
- The bottom line:
 - Consider vaccine in **ALL** patients >60 years of age
 - Vaccine is safe if patient is on MTX and low-dose prednisone
 - Advisable to delay biologic therapy until at least 2 weeks after the zoster vaccine is given

Rate of Zoster and PHN



ARTIS Registry: Overall Malignancy Rates in the General Population and Patients with RA

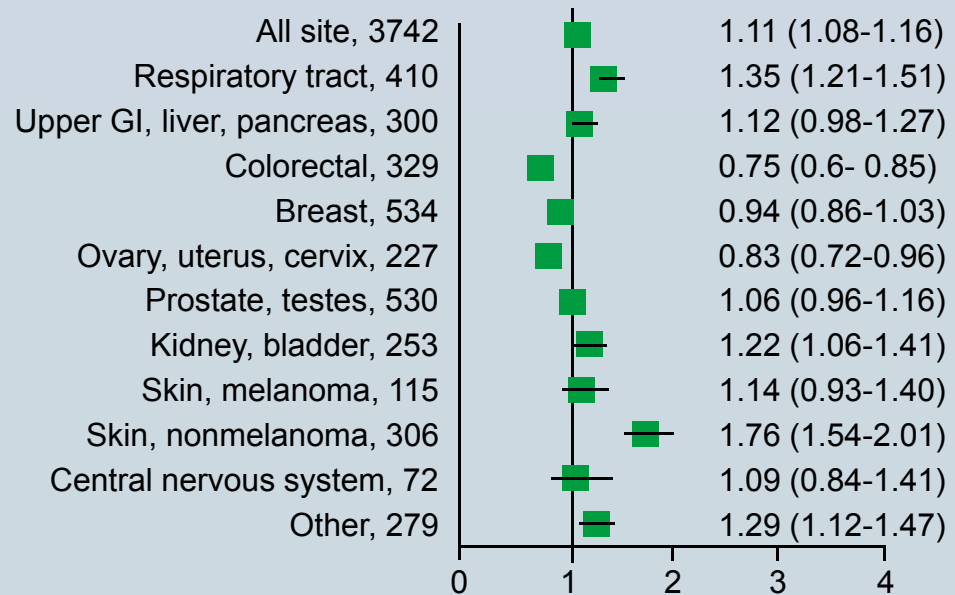
- RA cohort (N = 66,471; 0.7% of Swedish population) identified in 3 overlapping national registries (includes patients with RA stratified by either starting MTX, TNF inhibitors, or combination therapy)

Cancer in the General Population

Cumulative Risk by Age 75

Site	%
Any cancer	30
Prostate	14
Female breast	10
Colorectal	4
Lung	2.5
Lymphoma	1
Leukemia	0.7

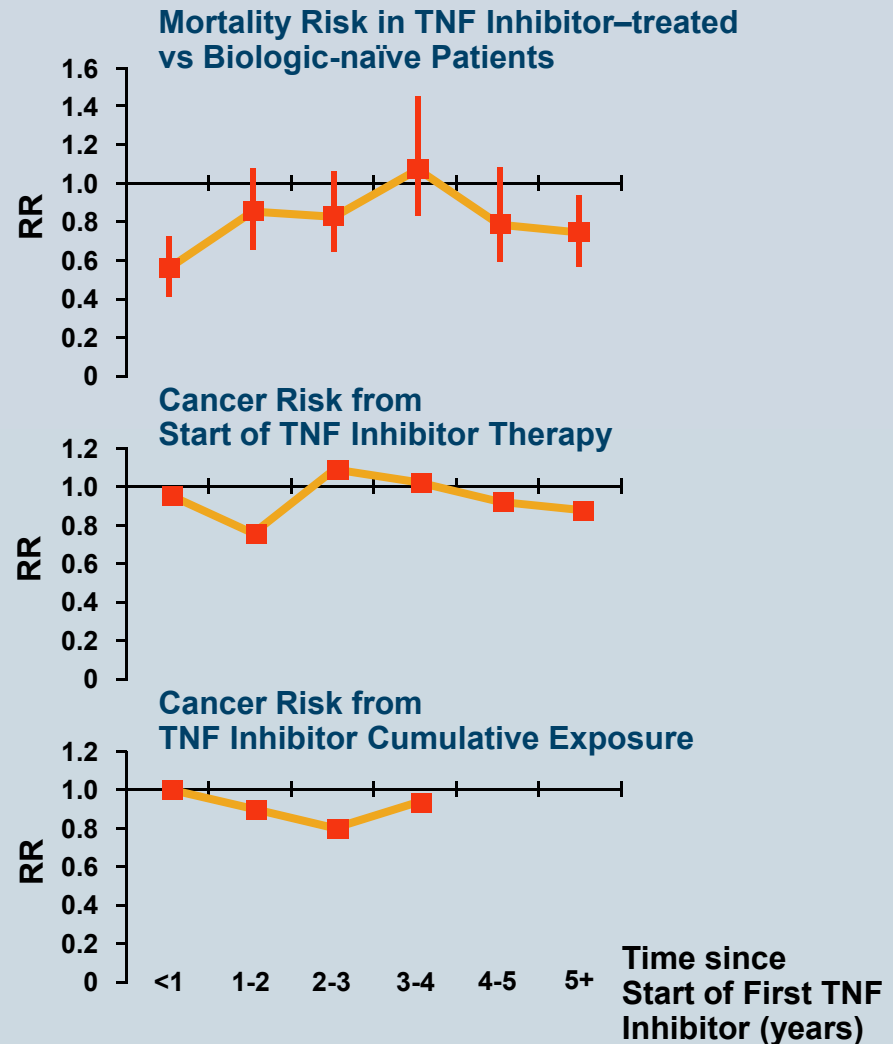
Cancer in Patients with RA Not Treated with Biologic Therapy: RR of Cancer in 66,471 Swedish Patients, 1998-2005



- Conclusion: certain cancers may be more common in RA patients not treated with TNF inhibitors**

ARTIS Registry: TNF Inhibitor Therapy in RA and Malignancy Risk

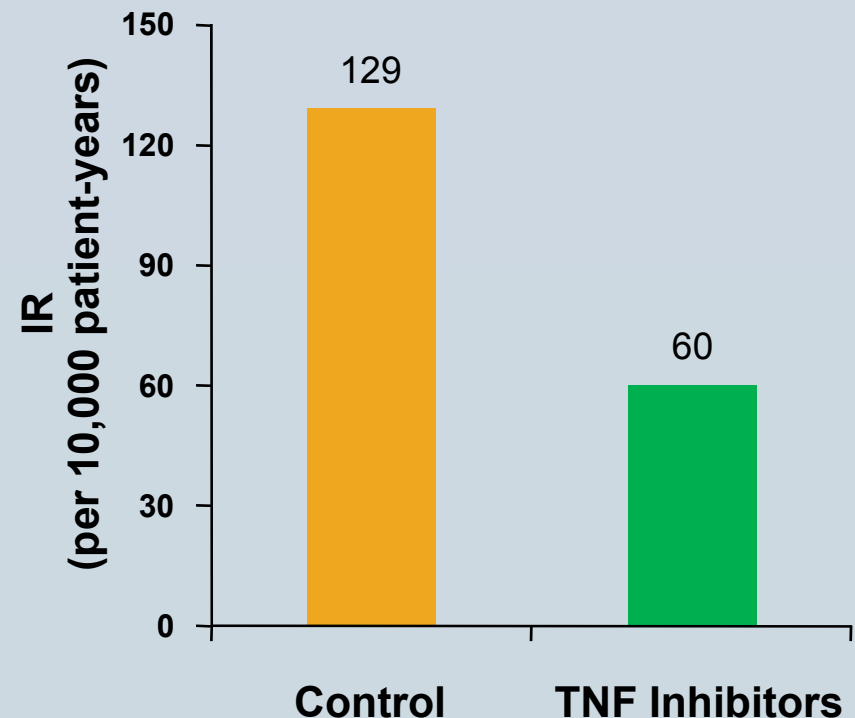
- National cohort of 66,995 patients from ARTIS registry taken between 1998 and 2006
- 6403 patients with RA identified as being treated with TNF inhibitors
- Patients followed up to 8 years to assess development of primary cancer
- **Conclusions**
 - Lower mortality risk among patients treated with TNF inhibitor therapy compared to biologic-naïve patients
 - Lack of trend in overall cancer risk following TNF therapy either from time since initiation or cumulative exposure



Is Malignancy Risk Higher in Patients with RA on TNF Inhibitor Therapy?

- Patients followed between 1999 and 2005 from BIOBADASER (national drug registry) and EMECAR (external RA cohort)
- Total follow-up of 14,001 patient-years (11,758 patients from BIOBADASER and 2243 patients from EMECAR)
- After adjusting for age, sex, disease duration, and disease activity, IRR was 0.92 (95% CI: 0.41-2.04), which was not statistically significant
- **Conclusion: TNF inhibitor therapy was not associated with higher risk for developing malignancy**

IR of Malignancies among Patients on TNF Inhibitor Therapy



IR = incidence rate.

Abasolo L, et al. Presented at: 2008 American College of Rheumatism (ACR) Annual Scientific Meeting; October 24-29, 2008; San Francisco, CA. Abstract 1266.

Risk of Skin Cancer in TNF Inhibitor Treated-Patients with RA

- Cross-linked ARTIS register, Swedish Cancer register, and national registers to establish RA cohort (n=67,845)
- Determined time-dependent melanoma and squamous cell cancer risk in TNF inhibitor-treated patients with RA

Relative Risk for Malignancy in Patients with RA Treated with TNF Inhibitors

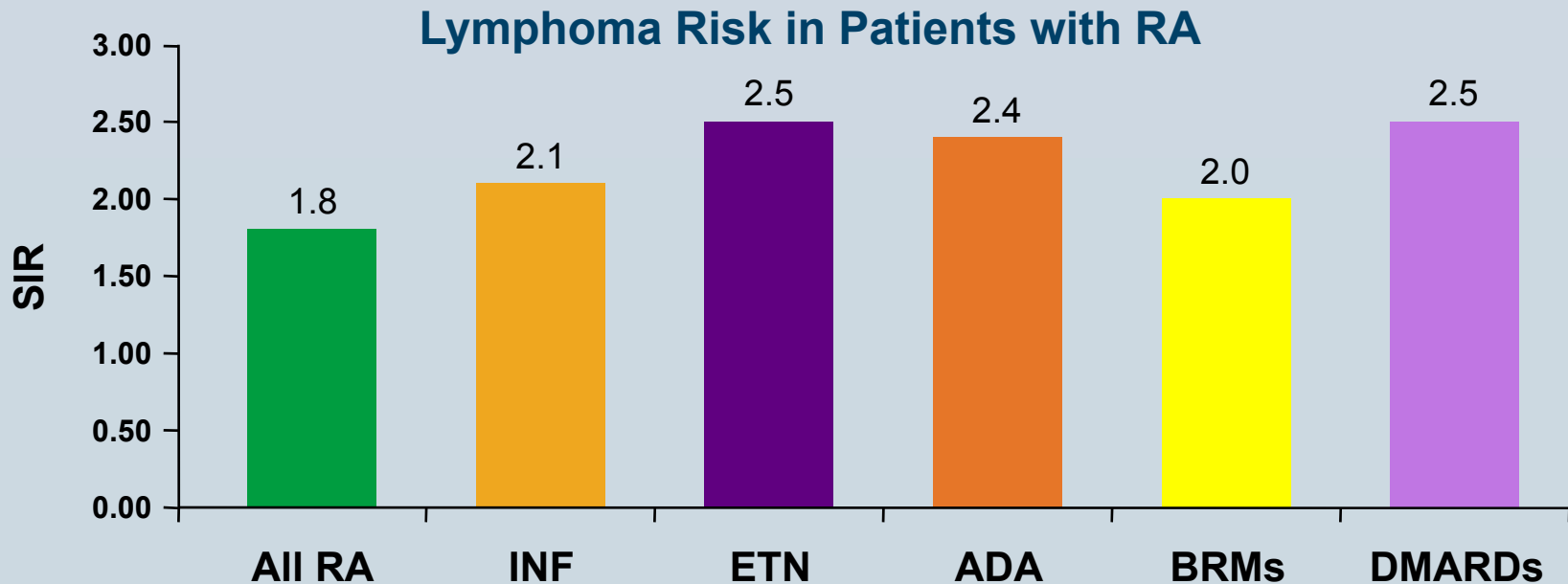
Cancer	Overall	<1 Year	1-3 Years	≥4 Years
All sites (RR, 95% CI, n)	1 (0.9-1.2), 240	1.1 (0.8-1.4), 56	1 (0.8-1.2), 123	1 (0.8-1.3), 61
Malignant melanoma (RR, 95% CI, n)	1.7 (1-2.9), 15	0.5 (0.1-3.5), 1	2.5 (1.4-4.8), 11	1.1 (0.3-2.5), 3
Squamous cell cancer (RR, 95% CI, n)	1.2 (0.8-2.0), 17	2.1 (0.8-5.1), 5	1.2 (0.6-2.3), 8	0.9 (0.3-2.4), 4

Conclusions:

- Overall risk of squamous cell cancer not increased
- Overall relative risk is slightly higher for melanoma, although the number of cases is low in this group of patients

Risk of Lymphoma among Patients with RA

- Lymphoma incidence from 1998 to 2005 assessed in United States:
 - 22,096 patients with RA
 - 6229 patients with noninflammatory musculoskeletal disorders
- SIR was based on age- and sex-adjusted comparisons to the SEER database

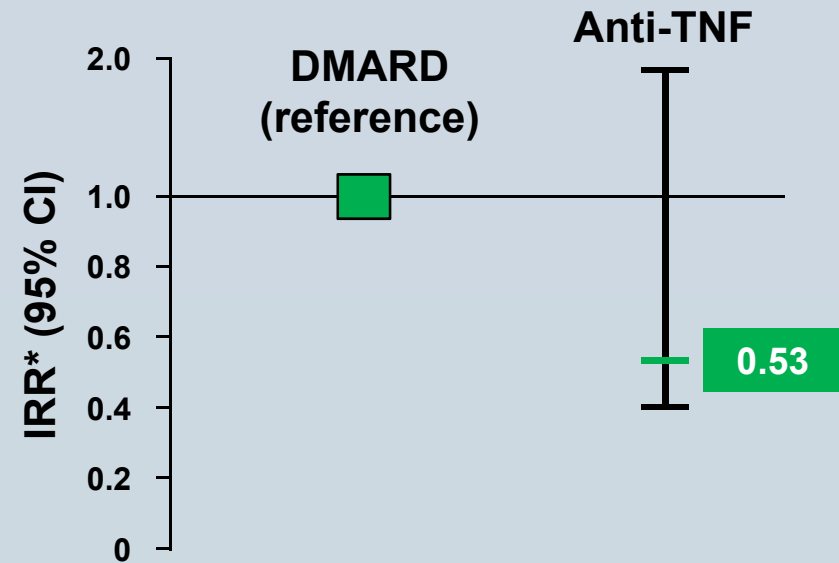


- **Conclusion: no statistically significant increase in risk of lymphoma associated with specific RA treatments, including biologic therapy**

BSRBR: Malignancy Incidence in Patients with RA and a Prior Malignancy

- Prior malignancy
- 177/10,735 (1.6%) TNF inhibitor-treated patients
 - 13 incident cancers in 11 patients (IR 25.3 per 1000 patient-years) (95% CI: 13.4-43.2)
- 118/3236 (3.6%) DMARD-treated patients
 - 10 incident cancers in 10 patients (IR 41.9 per 1000 patient-years) (95% CI: 20.1-77.1)
- Prior melanoma
- 17 TNF inhibitor-treated patients
 - 3 incident cancers in 3 patients
- 10 DMARD-treated patients
 - 0 incident cancers in 0 patients
- **Conclusion: patients treated with TNF inhibitors did not have a significantly higher IRR compared to patients treated with DMARDs**

IRR of Malignancy



*Adjusted for age and sex.

Dixon WG, et al. Presented at: 2008 ACR Annual Scientific Meeting; October 24-29, 2008; San Francisco, CA. Abstract 1264.

Malignancy in Patients with RA Treated with ABA

- 4134 patients with RA treated with ABA in 7 trials and 41,529 patients with RA treated with DMARD therapy in 5 observational cohorts (not postmarketing data)
- Evaluated incidence of malignancy for patients treated with ABA in different populations

	PBO DB	ABA DB	ABA 5 Core RA RCTs (DB + OL)*	ABA Cumulative (DB + OL)
Patients (n)	989	1955	2689	4134
Patient-years of follow-up (n)	794	1688	7282	8388
Total malignancies (excluding nonmelanoma skin) (n; CI)	5 0.63 (0.26-1.5)	10 0.59 (0.32-1.1)	46 0.63 (0.46-0.84)	51 0.61 (0.45-0.80)
Breast cancer (n; CI)	2 0.25 (0.06-1.01)	1 0.06 (0.01-0.43)	5 0.07 (0.02-0.16)	7 0.08 (0.03-0.17)
Colorectal cancer (n; CI)	0	0	2 0.03 (0.00-0.10)	2 0.02 (0.00-0.09)
Lung cancer (n; CI)	0	4 0.24 (0.09-0.64)	13 0.18 (0.10-0.31)	13 0.15 (0.08-0.27)
Lymphoma (n; CI)	0	1 0.06 (0.01-0.43)	4 0.05 (0.01-0.14)	5 0.06 (0.02-0.14)

- **Conclusion: IR comparable among RA patient populations treated with ABA**

*Includes the 5 core RA studies: Abatacept Trial in Treatment of Anti-TNF INadequate responders, Abatacept Study of Safety in Use with other RA thErapies, Abatacept in Inadequate responders to MTX, and 2 phase 2 studies. DB = double-blind; RCTs = randomized controlled trials; OL = open-label. Simon TA, et al. *Ann Rheum Dis*. 2008. [Epub ahead of print]

Morbidity and Mortality from MI in RA

- Evaluated occurrence of MI prior to RA diagnosis, relative risk of incident MI, death from MI, and all-cause mortality at RA diagnosis and onward
- 7653 patients identified from Swedish RA register (ongoing since 1995)
- 5 individuals from general population selected for each patient with RA (n=37,837)

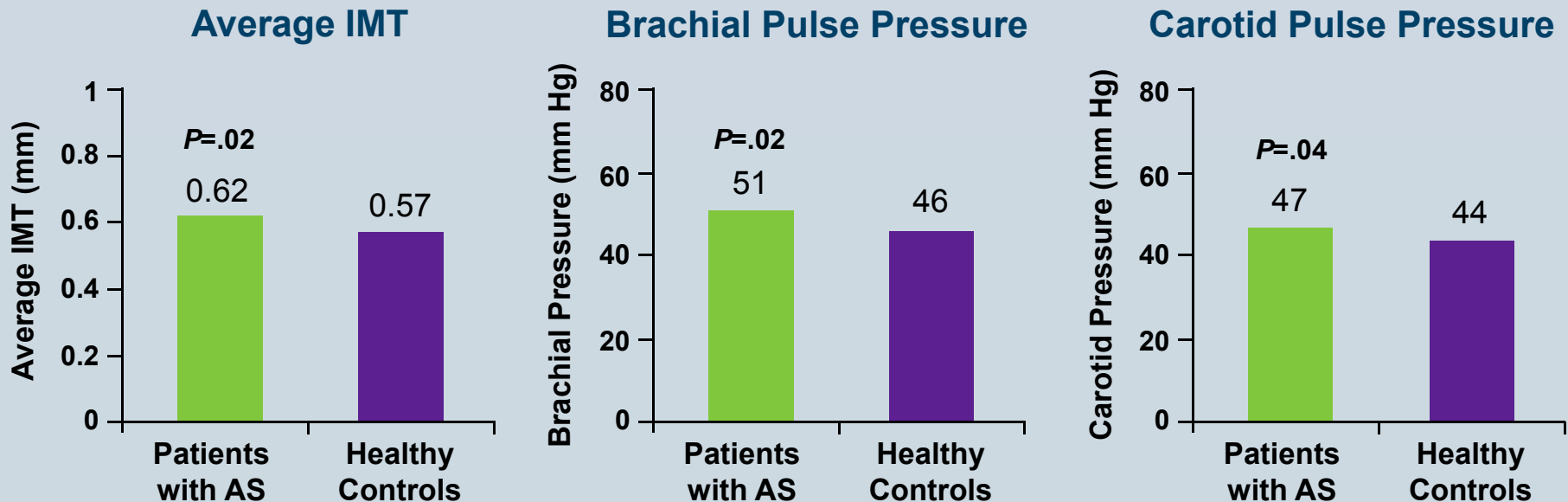
Relative Risk of Hospitalization with MI, Death from MI, and Death from All Causes

Outcome	From RA Diagnosis Onwards—Overall	<1 Year since RA Diagnosis	1-4 Years since RA Diagnosis	5-10 Years since RA Diagnosis
Hospitalization for acute MI	1.6 (1.4, 1.9) 227/676	1.4 (0.9, 2) 33/114	1.7 (1.4, 2.1) 131/370	1.7 (1.3, 2.3) 62/187
Death from MI	1.1 (0.8, 1.5) 49/196	1.3 (0.6, 2.6) 9/34	1 (0.6, 1.6) 21/100	1.1 (0.6, 2) 13/61
Death from any cause	1 (0.9, 1.1) 430/210	0.7 (0.5, 0.9) 56/384	1 (0.9, 1.1) 245/116	1.1 (1, 1.4) 128/550

- **Conclusion: prior to diagnosis, patients with RA are not at an increased risk of MI; this risk of MI increases rapidly after diagnosis, supporting a link to systemic inflammation rather than genetic factors**

Atherosclerosis Risk in Patients with AS May Be Similar to the Risk in RA

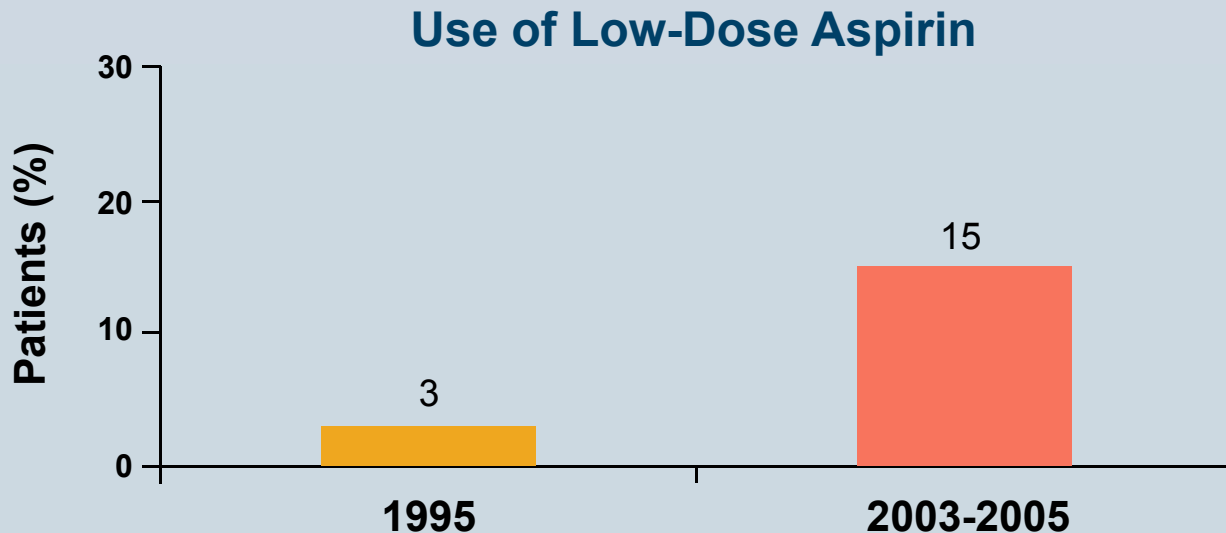
- 59 patients with AS treated with ETN therapy and 30 healthy controls
- Evaluated presence of subclinical atherosclerosis (assessed by average IMT) and arterial stiffness
- Differences remained after adjustments made for cardiovascular risk factors



- **Conclusion: AS was associated with subclinical atherosclerosis and vascular stiffness in these patients, suggesting a potential for increased clinical cardiovascular disease in patients with AS**

Low-Dose Aspirin in Patients with RA

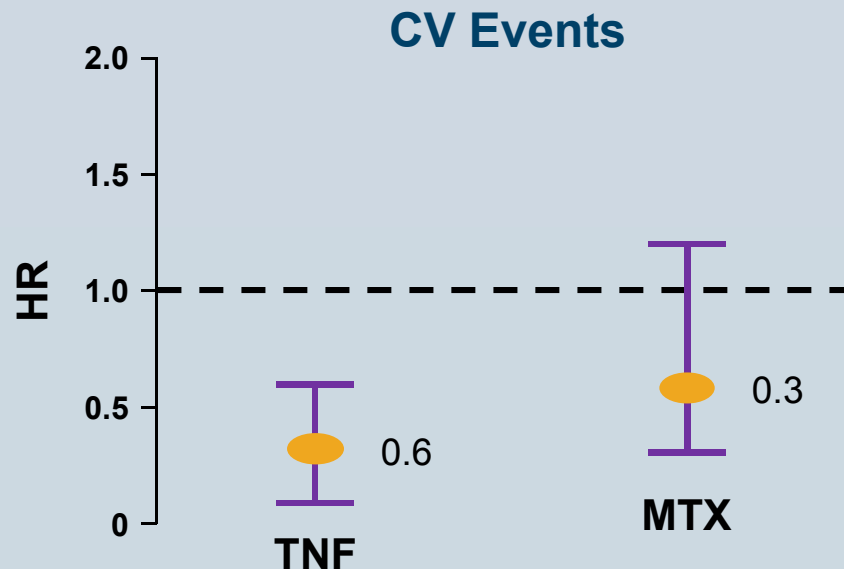
- Examined low-dose aspirin ($\leq 325\text{mg}$) use in a large population-based cohort of patients with RA ($n=27,761$)
- Approximately, only 1 in 5 patients who were 65 years of age or older received low-dose aspirin from 1995 to 2005
- Use of low-dose aspirin increased over time



- **Conclusion: despite improvement over time, the use of low-dose aspirin remains inadequate based on the enhanced risk for CAD in patients with RA**

TNF Inhibitor Therapy in RA and CV Outcomes

- Examined 10,870 patients with RA from CORRONA registry
 - Median RA duration: 7 years
 - Median follow-up: 2 years



- **Conclusions**

- Substantial reduction in CVD risk for patients treated with TNF inhibitors (RR 0.3)
- Intermediate reduction in CVD risk for patients treated with MTX (RR 0.6)
- Prednisone is an independent risk factor for CVD

Preventing Adverse Events in Patients with RA on Disease Modifying Therapy

- Infections

- Screen and monitor for bacterial infections, fungal infections, TB, herpes zoster infection, Hepatitis B and C
- Avoid use of biologic agents at least 1 week before and after surgery (data not evidence-based)

- Malignancy

- Are there any methods to monitor patients for the occurrence of malignancy?
- Is regular monitoring for malignancy appropriate?

- CVD

- Screen lipid panel and examine baseline cardiac function



Safety of Biologic Therapy in Rheumatic Diseases: Conclusions

- There is a small increased risk of SIEs in large, observational cohorts but not in RCTs
 - This difference is explained by patient selection, comorbidities, and concomitant drugs
- Opportunistic infections are rare in patients with RA on TNF inhibitors but have unusual presentations and high mortality
- No clear malignancy signal, but total length of exposure is still short
 - Uncertainty about safety in patients with prior cancer remains as numbers are small
- Ongoing concerns regarding TB, fungal infections, Hepatitis B and C, pregnancy, congestive heart failure, and PML



Audience Response

The incidence rate of infections between patients treated with DMARD therapy and those treated with biologic therapy is similar.

1. Strongly agree
2. Agree
3. Somewhat agree
4. Somewhat disagree
5. Disagree
6. Strongly disagree

Patient Case Presentation

- 35-year-old female presents with...
 - Pain and swelling of right wrist, several MCPs, MTPs, and right knee
 - AM stiffness for 45 minutes and PM fatigue
 - TJC = 13 and SJC = 12
- Medical history: Smoker (not considering pregnancy)
- Laboratory tests
 - RF+, anti-CCP+, ESR 54 mm/hr
- Radiograph of hand and wrist negative
- HAQ = 1.8 and DAS28 = 6.66



Patient Case Presentation (cont.)

- Treatment history
 - 8 months ago patient treated with MTX; dose escalated to 17.5 mg/week oral
 - 4 months ago a TNF inhibitor added and patient responded dramatically
 - 1 month ago patient notes nonproductive cough, increasing dyspnea and low-grade fever
 - Patient prescribed azithromycin, but has no response
- HRCT: possible LLL infiltrate
- MTX and TNF inhibitor stopped
- Bronchoscopy ultimately leads to positive culture for *Mycobacterium gordonae*
- Antibiotics changed and there is resolution of respiratory symptoms but RA flares

What is the best treatment for this patient at this time after the bacteria isolated was *Mycobacterium gordonae*?

1. Restart MTX and TNF inhibitor
2. Restart MTX alone
3. Switch to RTX
4. Switch to ABA
5. Switch to a different TNF inhibitor
6. Start low-dose prednisone

What is the best treatment for this patient at this time after the bacteria isolated was *Pseudomonas aeruginosa*?

1. Restart MTX and TNF inhibitor
2. Restart MTX alone
3. Switch to RTX
4. Switch to ABA
5. Switch to a different TNF inhibitor
6. Start low-dose prednisone

What is the best treatment for this patient at this time after the bacteria isolated was *Staphylococcus aureus*?

1. Restart MTX and TNF inhibitor
2. Restart MTX alone
3. Switch to RTX
4. Switch to ABA
5. Switch to a different TNF inhibitor
6. Start low-dose prednisone