MANCHESTER 1824

The University of Manchester

Serious infections in rheumatoid arthritis: Is there a problem or not?

DANBIO 10 years
Copenhagen, 9th Sept 2011

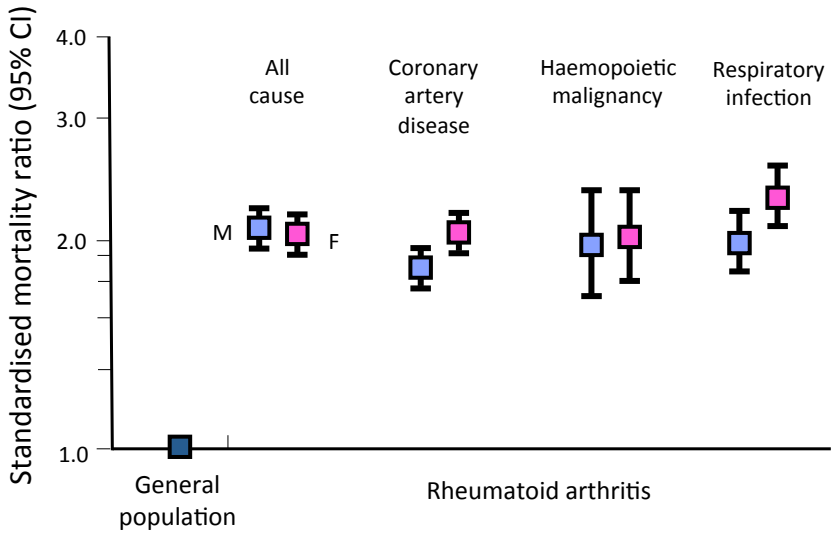
Will Dixon

Arthritis Research UK Epidemiology Unit

MRC Medical Research Council

Mortality in patients with RA

Mortality in patients with RA



Thomas et al. J Rheum 2003, 30 (5)

Serious infections in rheumatoid arthritis: Is there a problem or not?

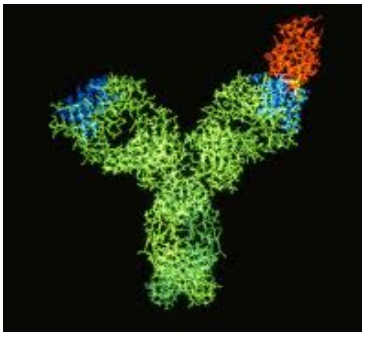
Yes

Reason for increased infection risk

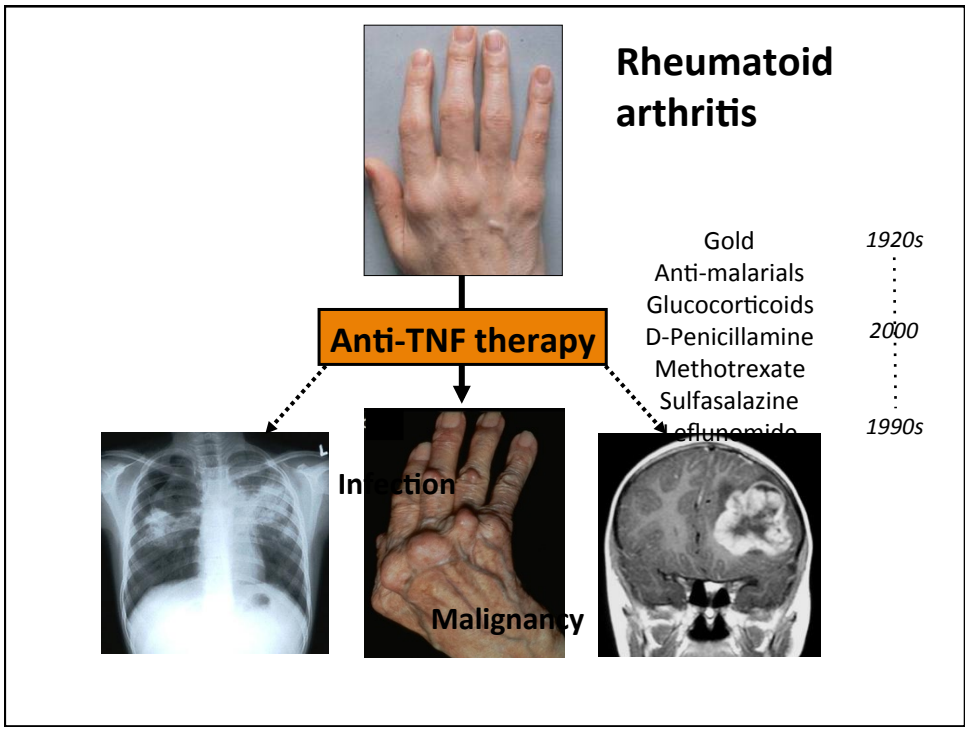
- Disease itself
  - Immune changes; damage; disability
- Shared risk factors
  - Smoking
- Immunosuppression
  - Glucocorticoids
  - Traditional DMARDs
  - Biologics

Reason for increased infection risk

Glucocorticoid therapy
1950-present



Anti-TNF therapy
2000-present



Review

European biologicals registers: methodology, selected results and perspectives

A Zink,[1] J Askling,[2,3] W G Dixon,[4] L Klareskog,[3] A J Silman,[4] D P M Symmons[4]

British Society for Rheumatology Biologics Register (BSRBR)[2 6 12 18 21–24]

German Biologics Register (RABBIT)[5 25–27]

Swedish Biologics Register (ARTIS)[7 28–31]

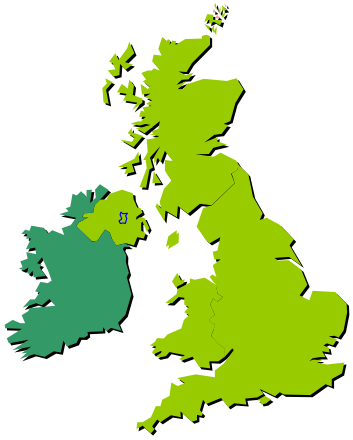
Spanish BIOBADASER register[8 10 32–35]

Danish Rheumatologic database (DANBIO)[36–40]

Norwegian DMARD register (NOR-DMARD)[41–44]

BSR Biologics Register

- Prospective cohort of **ALL** UK patients treated with anti-TNF therapy for RA
- Commenced 2001
- Biologic-naïve at registration
- 20,000 patients recruited

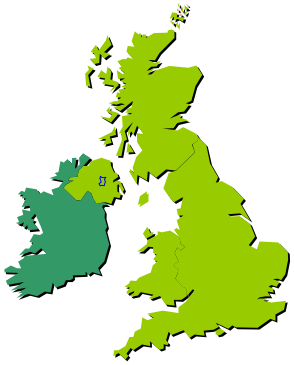


NHS National Institute for Clinical Excellence

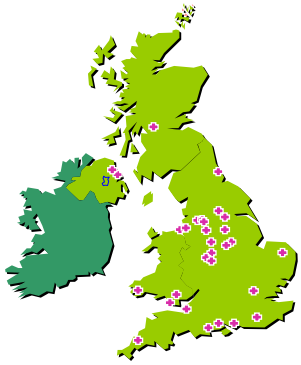
"All clinicians prescribing anti-TNF therapy for RA should (with the patient's consent) register the patient with the BSRBR"

Study design

Incidence of serious adverse events



VS



Anti-TNF treated RA cohort (n=4000)
- Infliximab
- Etanercept
- Adalimimab

Biologic-naïve active RA cohort (n=4000)

Hypothesis

- Anti-TNF therapy associated with an increased incidence of serious infection
  - Hospitalisation
  - IV antibiotics
  - Death

Baseline characteristics

	DMARD	Anti-TNF
Number of patients	2170	8659
Mean age: Years (SD)	60 (12)	56 (12)
Females: %	72	76
Median disease duration: Years (IQR)	7 (1-15)	12 (6-19)
Disease activity: • Mean DAS28 score (SD) • Mean HAQ (SD)	 5.0 (1.4) 1.5 (0.8)	 6.6 (1.0) 2.1 (0.6)

Data to 2006

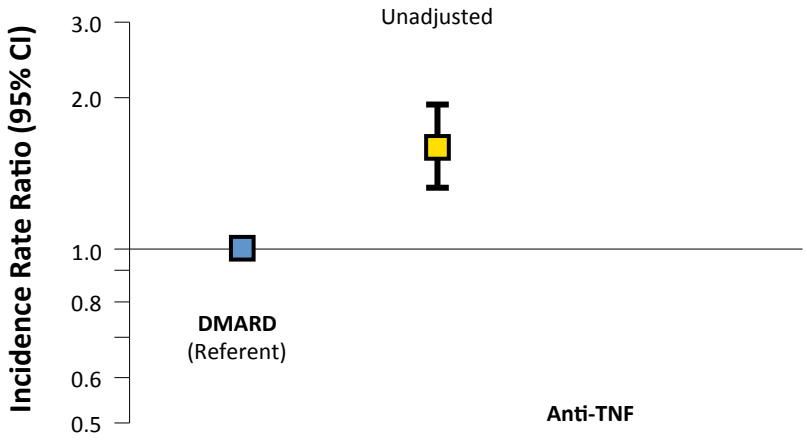
Dixon et al. A&R, 2007, 56(9)

All-site serious infection

	DMARD (n=2170)	Anti-TNF (n=8659)
Person years (pyrs)	2908	13277
Number of infections	114	737
Rate /1000pyrs	39.2	55.5

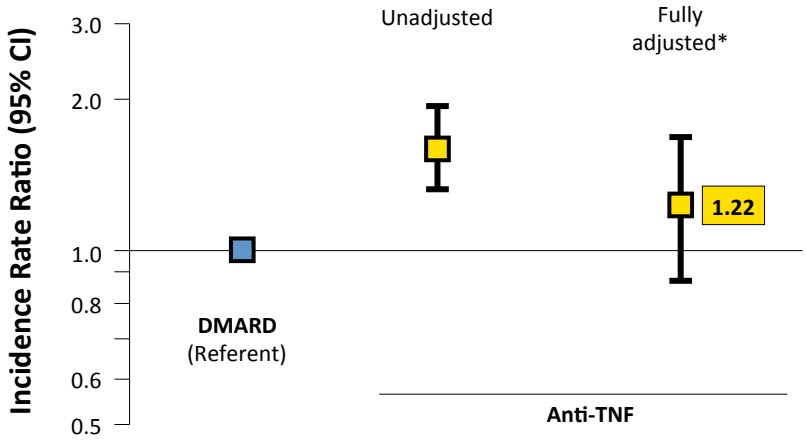
Dixon et al. A&R, 2007, 56(9)

All-site serious infection



Dixon et al. A&R, 2007, 56(9)

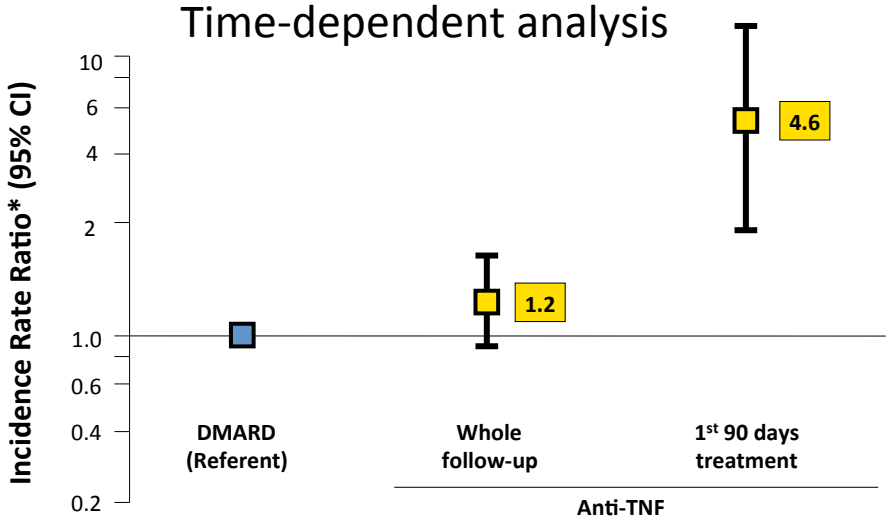
All-site serious infection



* Adjusted for age, gender, disease severity, co-morbidity, extra-articular manifestations, baseline steroid use and smoking

Dixon et al. A&R, 2007, 56(9)

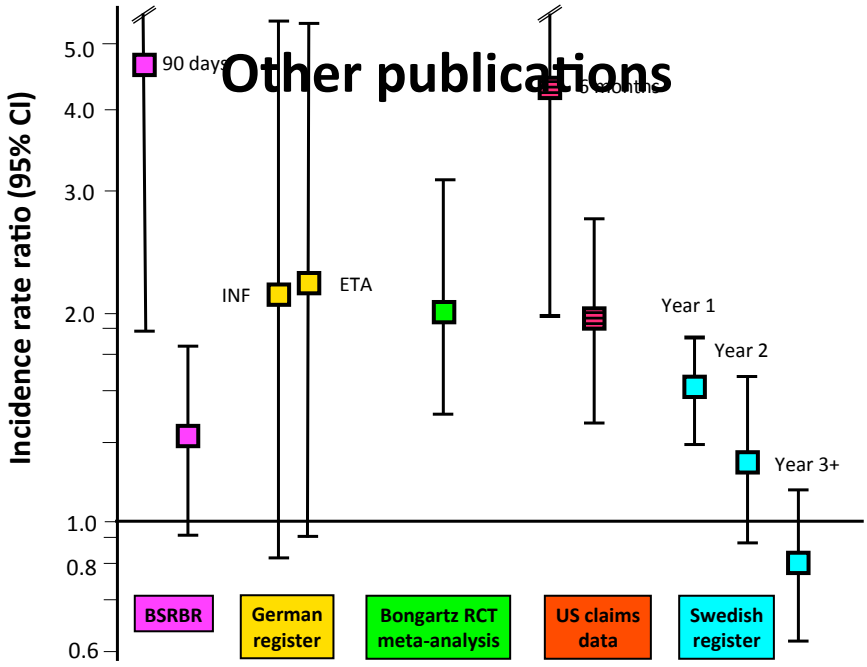
All-site serious infection
Time-dependent analysis



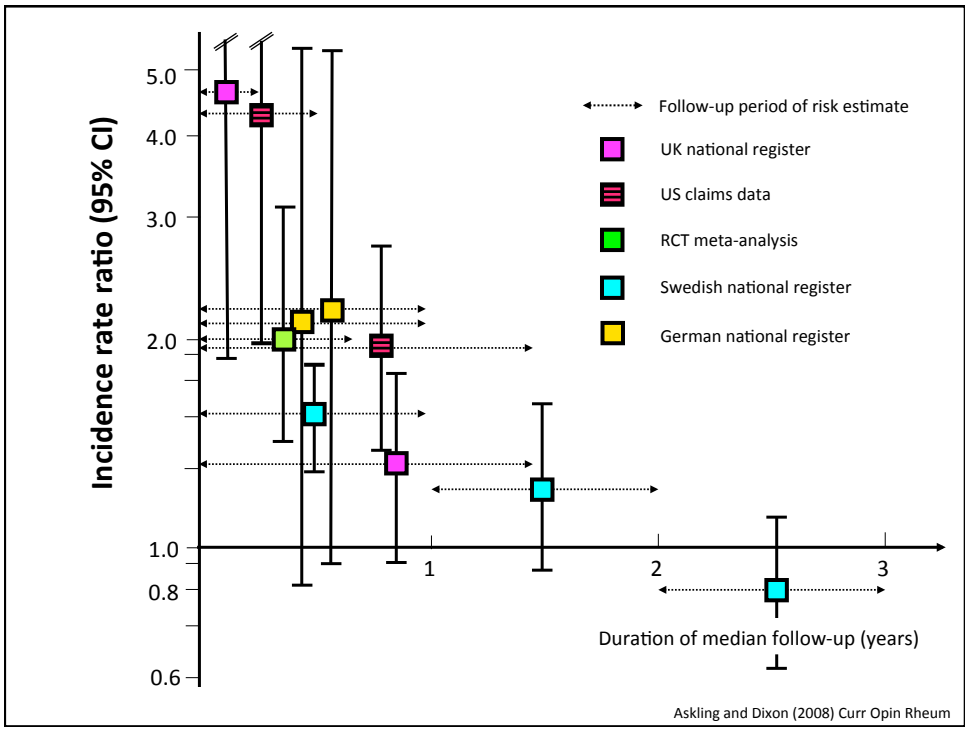
* Adjusted for age, gender, disease severity, co-morbidity, extra-articular manifestations, baseline steroid use and smoking

Dixon et al. A&R, 2007, 56(9)

Other publications



David Shrigley



Askling and Dixon (2008) Curr Opin Rheum

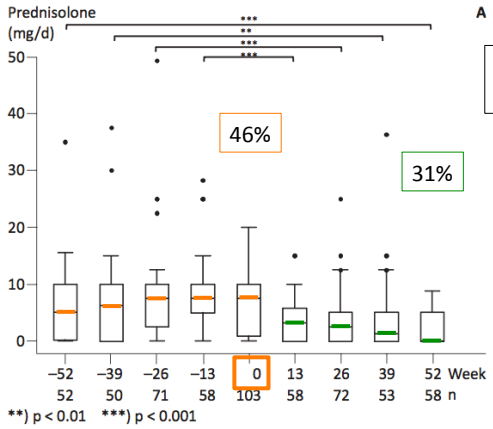
Possible explanations for risk pattern

- Susceptible group of individuals
- Improvement in disease activity
- Low threshold for iv antibiotics early in anti-TNF use
- "Depletion of susceptibles"
- Differential use of steroids pre- and post anti-TNF

Dan Med Bul 58/4 | April 2011 DANISH MEDICAL BULLETIN | 1

Tumour necrosis factor-α inhibitors are glucocorticoid-sparing in rheumatoid arthritis

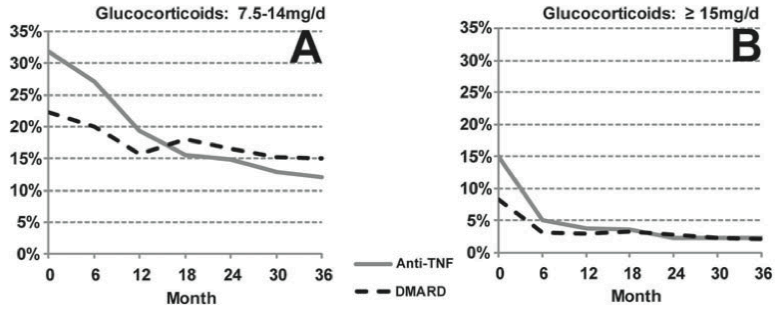
Anna Christine Nilsson, Anne Friesgaard Christensen, Peter Junker & Hanne Merete Lindegaard



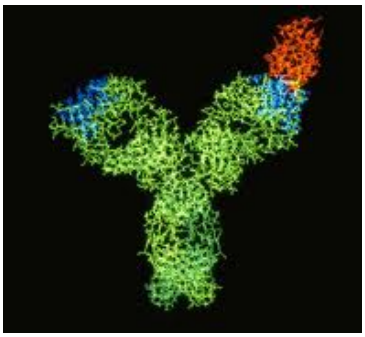
Proportion of patients using oral GCs

Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient?

A Strangfeld,[1] M Eveslage,[1] M Schneider,[2] H J Bergerhausen,[3] T Klopsch,[4] A Zink,[1,5] J Listing[1]



Glucocorticoid therapy
1950-present



Anti-TNF therapy
2000-present

Safety of glucocorticoid therapy

Frequency?

Dose effect?

Stopping?

At risk?

EXTENDED REPORT

EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases

J N Hoes, J W G Jacobs, M Boers, D Boumpas, F Buttgereit, N Caeyers, E H Choy, M Cutolo, J A P Da Silva, G Esselens, L Guillevin, I Hafstrom, J R Kirwan, J Rovensky, A Russell, K G Saag, B Svensson, R Westhovens, H Zeidler, J W J Bijlsma

Ann Rheum Dis 2007;66:1560–1567. doi: 10.1136/ard.2007.072157

Recommendation 1:

The adverse effects of glucocorticoid therapy should be considered and discussed with the patient before glucocorticoid therapy is started.

Frequency of adverse events

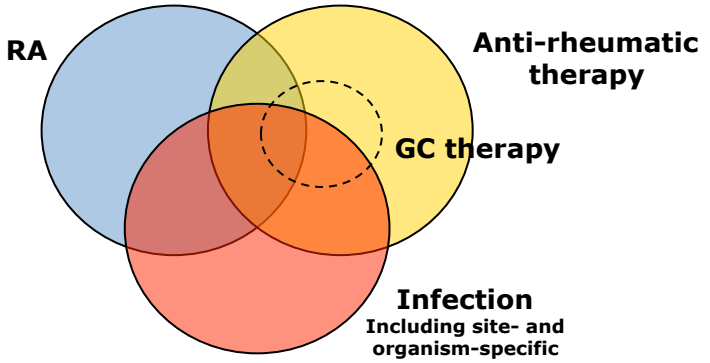
- Infection
- Cardiovascular disease e.g. MI
- Gastro-intestinal e.g. dysp
- …et diabetes
- Weight gain
- Cat…
- …eoporosis
- Fractures
- Purpura, skin tears

Dose, duration, age, gender, pre-existing co-morbidity, …

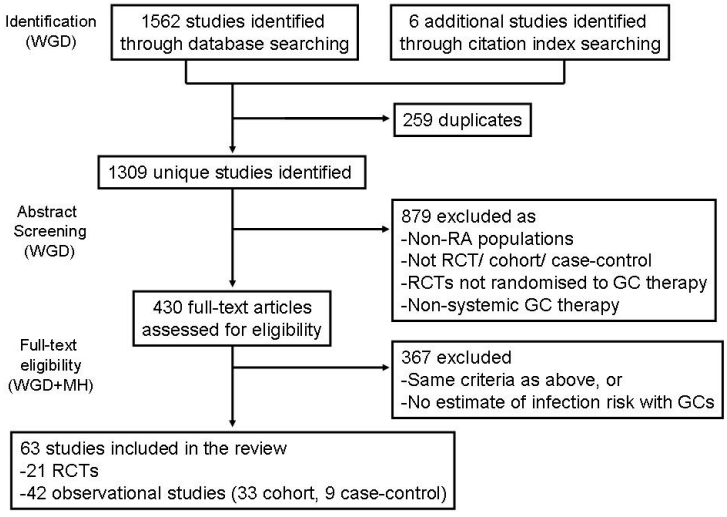
very common	(>1/10 patients)
common	(>1/100)
uncommon	(>1/1000)
rare	(>1/10 000)
very rare	(>1/100 000)

Systematic review of infection with GCs

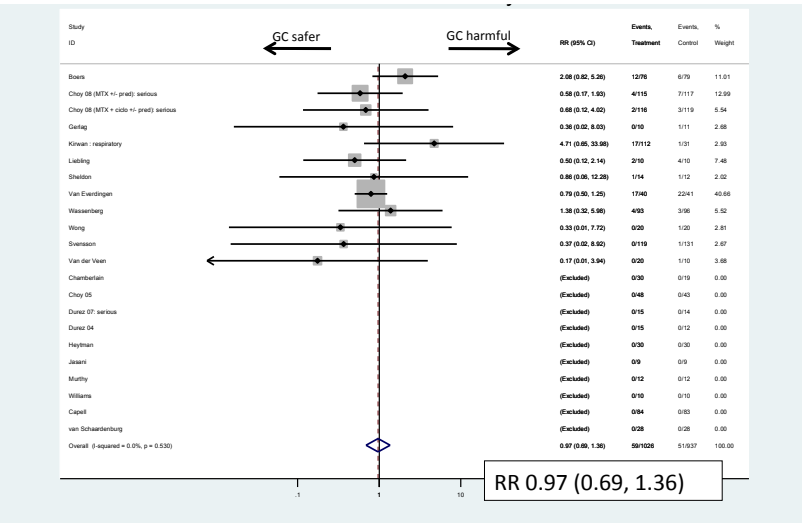
1. All RCTs of systemic GC therapy in RA
2. All observational studies examining influence of systemic GC therapy on risk of infection



Systematic review of infection with GCs



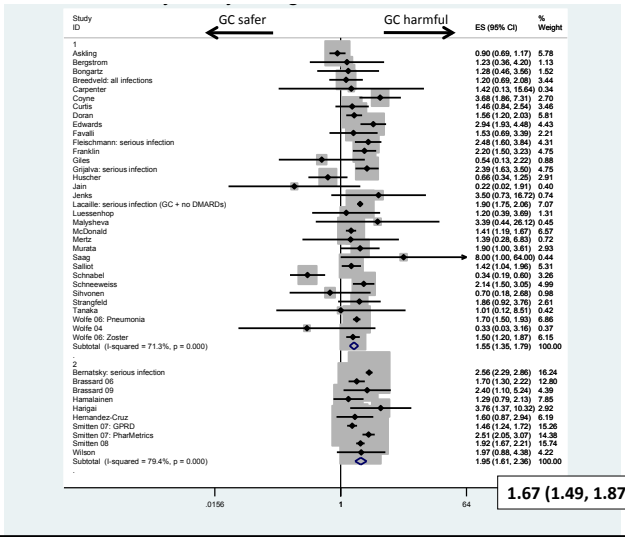
Systematic review & meta-analysis
Randomised controlled trials



Methodological challenges

- RCTs
  - Low numbers of patients (~1000 per arm)
  - Quality of safety reporting (methods and results)
  - Variable definition of infection

Systematic review & meta-analysis
Observational studies



Systematic review & meta-analysis
Methodological challenges

- RCTs
  - Quality of safety reporting
  - Variable definition of infection
- Observational studies
  - Heterogeneity
    - Definition of GC exposure
    - Duration of exposure
    - Risk attribution models
    - Adjustment for confounders
  - Publication bias

Systematic review & meta-analysis
Summary

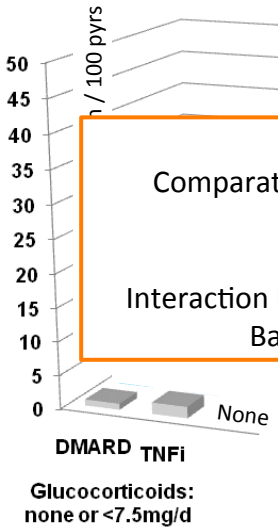
- No clear message about risk of infection
  - Low confidence in summary measures
- No increased risk to <1.6x increase

Scenario

- 68 year old woman with RA
- DAS28 6.4
  - Failed MTX, SSZ, LEF
- Diabetic
- Two admissions with infection
- What is her risk of infection with treatment options?

Personalised risk

RABBIT
www.biologika-register.de



Unanswered questions
Comparative safety across all drug therapies
Impact of dosage
Risk on stopping therapy
Interaction between drugs and other risk factors
Balancing benefits and harms

One or two:	Age > 60 Chronic lung disease Chronic renal disease >5 DMARDs at baseline	RR=1.6
Three:	2 + past history of serious infection	

Strangfeld et al. ARD, 2011

Solution

- Large population datasets
- High quality information on
  - Exposures: Dosage, start and stop dates
  - Outcomes: Validity
  - Confounders: Disease severity
- Collected from operational clinical practice

DANBIO
DANSK REUMATOLOGISK DATABASE