Infections and Biologics

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Pioneering better health for all

Overview

- What is the risk of infection with biologics?
- Are some patients at greater risk?
- Are some drugs safer?

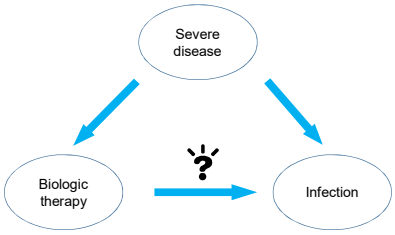
Case scenario

- You recently commenced Judith, a 54 year old teacher with seropositive rheumatoid, on Certolizumab-pegol.
- Eight weeks after starting treatment, she is admitted with sepsis.
  - Was the drug to blame?

Rheumatoid arthritis and infection

- Around 3–5% of people with RA will experience a serious infection each year
- Rates of infection exceed that of the general population (matched for age and sex)
  - Sepsis incidence: 50% higher
- Explanations for this are complex
  - Disease
  - Drugs

Rheumatoid arthritis



Understanding causality

Relationship between disease activity and infection risk

DAS	Infection rate / 100 pyrs
<5	2.7 (2.1 to 3.5)
5	3.0 (2.5 to 3.6)
6	4.2 (3.7 to 4.8)
7	4.3 (3.7 to 5.0)
>7	6.4 (4.8 to 8.3)

Emery Clin Exp Rheum 2014 (32: 653-660)

Overall risk of serious infection

Results		DMARD cohort	Anti TNF
Follow-up, patient-years		9,259	36,230
Number of serious infections		296	1512
Incidence / 100 patient-years (95% CI)		3.2 (2.8–3.6)	4.2 (4.0–4.4)
Unadjusted hazard ratio (95% CI)		Referent	1.5 (1.3–1.7)
Adjusted hazard ratio (95% CI)			1.2 (1.1–1.5)
	0 – 6		1.8 (1.2–2.6)
Time varying risk:	6 – 12		1.4 (0.9–2.0)
Follow-up time window, months	12 – 24		1.2 (0.8–1.6)
	24 – 36		0.9 (0.6–1.3)

Rheumatology 2011; 50: 124-31

Attributing risk to TNF inhibitors

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Rheumatology 2011; 50: 124-31

BSRBR-RA results in comparison with RCTs

- Meta analysis of 18 RCTs
  - 8808 patients included
- Incidence of serious infection: 3.3%
  - No significant increase in risk of infection

OR 1.21; 95% CI 0.89 to 1.60

Leombruno et al. Ann Rheum Dis 2009; 68: 1136–114

Absolute versus relative risk

- NNtT = one over the absolute risk difference
- Assume background risk 5% / year
- HR 1.2 equates to an absolute risk 6%
- NNtT to see one additional infection

= 100

Case

- Colin is a 40 year old man with rheumatoid who has been in remission for 18 months now, since starting adalimumab.
- He recently read an article about the risk of infection with biologics, and was concerned about remaining on anti-TNF therapy.

Time varying risk (survivorship bias)

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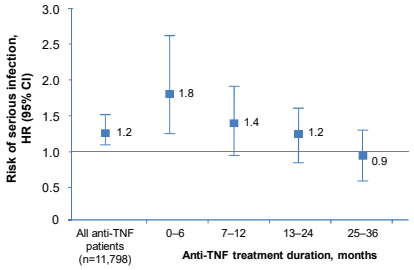
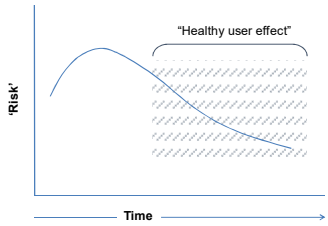
Rheumatology 2011; 50: 124-31

Time-dependent risk (BSRBR data)



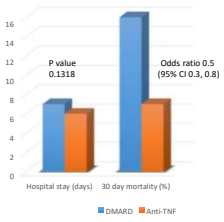
Modelling risk over time



Clinical relevance of time varying risk

- What should you say to Colin?

Infection severity



Rheumatology 2011; 50: 124-31

Case

- Doris is 82 years old. She has seropositive rheumatoid. Her DAS is 6.9 despite methotrexate and sulfasalazine.
- Should you:

a) Add in prednisolone
b) Switch methotrexate to leflunomide
c) Start an anti-TNF
d) Start half dose (500mg) rituximab

Contrasting age and frailty

(Born 1934)

Absolute versus relative risk

- NNtT = one over the absolute risk difference
- Assume background risk 20% / year
- HR 1.2 equates to an absolute risk 24%
- NNtT to see one additional infection

= 25

Absolute versus relative risk

- Remember that an 'average' risk may not equate to individual risk
- Special populations
  - Elderly
  - Steroids
  - Joint replacements
  - Co-morbidity

Predictors of infection (CORRONA data)

- In the era of personalised medicine, the search is on for markers that stratify patients
- Risk factors for serious infection have been studied in several registries, with consistent findings. The data from the CORRONA Registry presented this very clearly:

Risk factor	Incident Rate Ratio	95% CI
Prior hospitalised infection	16.2	8.0–32.8
Corticosteroids (>7.5 mg)	13.6	7.2–25.5
Disease activity (per 0.6 DAS-28 increment)	1.3	1.1–1.6
Increasing age (per 10-year increase)	1.3	1.0–1.6

Case

- Isabelle is a 29 year old woman with seropositive rheumatoid. She is on methotrexate 12.5mg weekly plus hydroxychloroquine.
- She has been unable to escalate the methotrexate dose because of recurrent urinary tract infections.
- Is there a 'safer' biologic option?

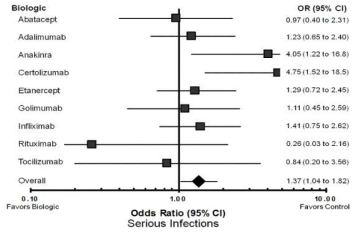
Patterns of infection

- Are the infections genuine (microbiologically confirmed)?
- Does the infection history correspond to a immunodeficiency phenotype?
- Are steroids implicated?
- Could there be an alternative explanation (diabetes)?

Comparing risk across other drugs

- Methodologically challenging
- Abatacept and etanercept appear to have lower infection risk
- Probably more important to understand why people are having recurrent infections

Comparative analyses between agents



Cochrane Database Syst Rev 2011: CD008794.

Challenges of studying risk with rituximab

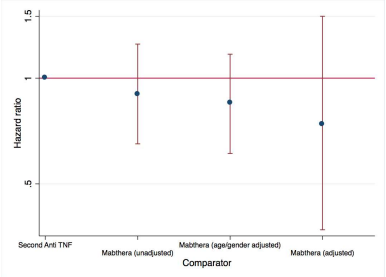
- Many publications are heavily biased by long term extension data from trials
- In observational studies, when do people stop being 'exposed' to the drug?

Serious infection with Rituximab

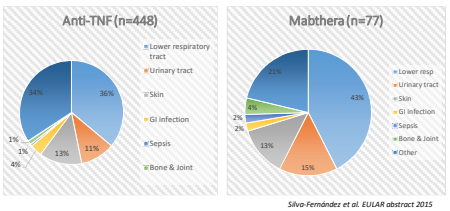
Results	Second Anti TNF	Rituximab
Follow-up, patient-years	2,688	866
Events	158	47
Median time to infection, years (IQR)	0.3 (0.2, 0.5)	0.3 (0.2, 0.5)
Incidence rate / 100 patient-years (95% CI)	6.0 (5.1, 7.0)	5.6 (4.2, 7.4)

Silva-Fernández et al. EULAR abstract 2015

Risk of serious infection with Rituximab

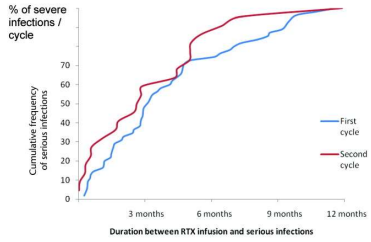


Causative organisms



Silva-Fernández et al. EULAR abstract 2015

Rituximab findings in AIR registry



Key predictor of infection: low IgG level (<6 gm/liter) before RTX treatment (OR 3.7 [95% CI 1.1–12.1], *P* = 0.03)

B cell depletion (Rituximab)

- Overall infection rates appear similar to TNFi
- Those at greatest risk can be identified by declining antibody levels
- Irreversible antibody deficiency can develop

Heusele et al. Clin Rheumatol (2014) 33:799–805

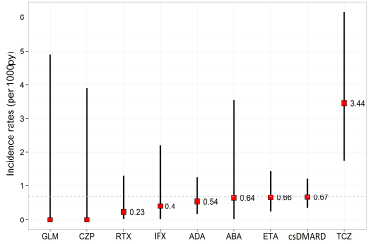
Case

- Gillian is a 60 year old woman with seronegative rheumatoid. She has had a primary failure to Benepali.
- Her current DAS is 7.1.
- She is on hydroxychloroquine only, having been intolerant to methotrexate (nausea) and sulfasalazine (rash).
- She is known to have diverticular disease.

Tocilizumab and diverticular perforations

- Blunted CRP response
- Delays in diagnosis
- Higher mortality

Tocilizumab and intestinal perforation



Abatacept infection predictors: ORA Registry

	Patients with severe infection (n=69)	Patients without severe infection (n=907)	HR univariate analysis (95% CI)	HR multivariate analysis (95% CI)
Previous serious or recurrent infection	37 (53.6)	298 (33.4)	2.30 (1.43 to 3.70)	1.94 (1.18 to 3.20)
Previous DMARDs, mean±SD	3±1.6	2.8±1.5	1.07 (0.91 to 1.26)	
Previous anti-TNF			0.55 (0.30 to 0.98)	
Previous rituximab	14 (20.3)	276 (30.5)	0.62 (0.34 to 1.11)	
IgG <6 g/L	2 (7.1)	19 (6.2)	1.28 (0.30 to 5.4)	
Concomitant DMARDs	41 (59)	589 (65)	0.88 (0.53 to 1.45)	
Concomitant corticosteroids	54 (83.1)	678 (75.8)	1.57 (0.82 to 3.00)	

Ann Rheum Dis 2016;75:1108-1113

Specific infections

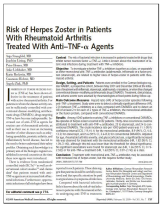
- There are several mechanistic reasons to expect differential risks of infection by both site and organism
- TNF is implicated in the cellular aspects of host defense
- Increased susceptibility to intracellular bacteria and viruses would be predicted
  - Tuberculosis is the example that we have all grown to know well

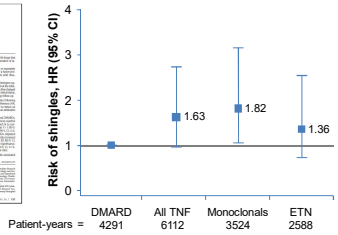
Rate of zoster/1000 person years (99% CI)

Population	<50	50-59	60-69	≥70
General population	2.08 (1.74 to 2.49)	4.37 (3.72 to 5.12)	6.69 (5.76 to 7.76)	8.84 (7.49 to 10.43)
Rheumatoid arthritis	3.51 (2.40 to 5.13)	6.35 (3.46 to 11.66)	9.96 (5.57 to 17.77)	12.47 (6.94 to 22.41)
SLE	6.32 (3.73 to 10.74)	8.67 (3.20 to 23.46)	8.20 (2.99 to 22.45)	11.36 (4.22 to 30.60)
COPD	2.31 (1.40 to 3.84)	5.62 (2.44 to 12.94)	9.19 (4.09 to 20.62)	11.54 (5.08 to 26.20)
Diabetes	2.66 (1.99 to 3.56)	4.84 (3.23 to 7.27)	6.79 (4.62 to 9.97)	8.55 (5.76 to 12.70)

Forbes et al. BMJ 2014;348:g2911

Shingles


Risk of Herpes Zoster in Patients With Rheumatoid Arthritis Treated With Anti–TNF-α Agents

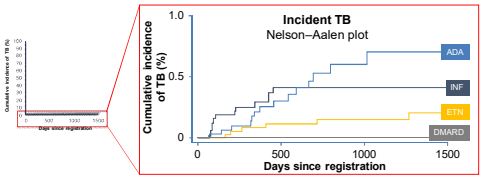


- Incidence rates: DMARD 5.9/1000; monoclonal anti-TNF: 11.1/1000

Opportunistic infections

- A typical manifestation of an unusual organism
  - Legionella, Listeria
- An unusual manifestation of a common organism
  - Multi-dermatomal zoster

Tuberculosis

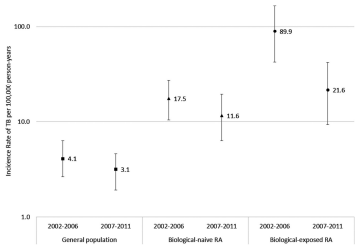


Drug	Registration (entry to study)	1 year (365 days)	2 years (730 days)	3 years (1095 days)	4 years (1460 days)
DMARD	3232	2652	1839	742	213
ETN	3913	3474	3051	2363	1020
INF	3295	2694	1918	1392	918
ADA	3504	2457	1531	729	247

Tuberculosis screening

- TB risk appears lower
  - May in part reflect screening procedures

Tuberculosis risk over time



Ann Rheum Dis 2015;**74**:1212-1217

Leishmania in Italy

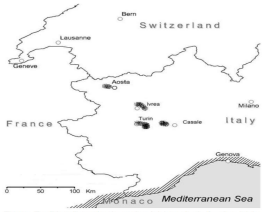


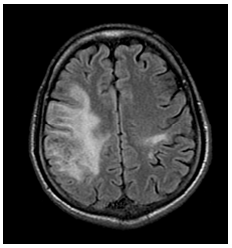
Figure. Traditionally endemic canine leishmaniosis (canine leishmaniasis) areas (slash marks) and new foci in continental climate areas of northwestern Italy (shaded areas).

Leishmania and TNFi

First author	Year of publication	Sex, age	Presen-tation	Type
Romani-Costa	2004	M, 55	VL	Infliximab
Fabre	2005	F, 53	VL	Infliximab
Bassetti	2006	F, 69	VL	Adalimumab
Bagalas	2007	F, 60	VL	Etanercept
Tektonidou	2008	M, 45	VL	Infliximab
Xynos	2009	F, 71	VL	Infliximab
Xynos	2009	M, 55	CL	Infliximab
Schneider	2009	F, 51	CL	Adalimumab
Balta-Cruz	2009	F, 56	MCL	Adalimumab
De Leonardis	2009	M, 63	VL	Infliximab
Mueller	2009	M, 31	CL	Infliximab
Garcia Vidal	2009	M, 55	VL	Infliximab
Jeziorski	2009	F, 7	VL	Etanercept/infliximab[a]
Kritikos	2010	F, 77	VL	Infliximab
Hakimi	2010	M, 50	CL	Infliximab
Moreno	2010	F, 72	VL	Adalimumab
Molto	2010	M, 60	VL	Adalimumab
Zanger	2011	M, 38	CL	Infliximab
Franklin	2009	F, 42	MCL	Adalimumab

Zanger et al. Clin Microbiol Infect 2012; 18: 670–676.

Progressive Multifocal Leukoencephalopathy



- Notoriety bias
- Estimated risk
  - 1:1,000,000

Calabrese et al. Arthritis Rheum. 2012 Sep;64(9):3043-51.

JAK inhibitors

- Licensed in US, not Europe yet
  - Concerns regarding safety
  - Shingles
  - Opportunistic infections
- Model disease to compare to?

Summary

- Biologics are associated with a small increase in infection risk
- Some patients are particularly vulnerable
- Some drugs may be (slightly) safer