Anti-TNF: similarities and differences

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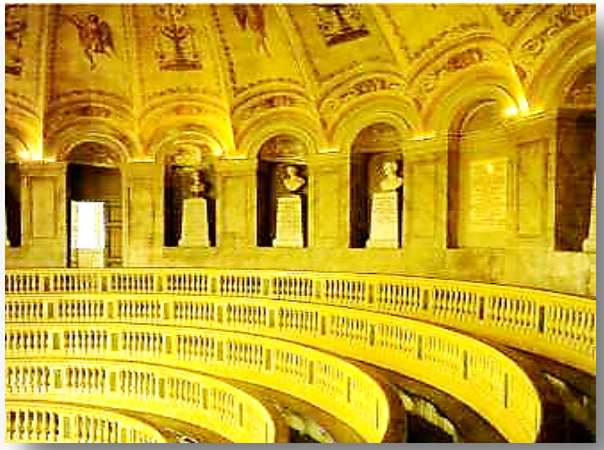
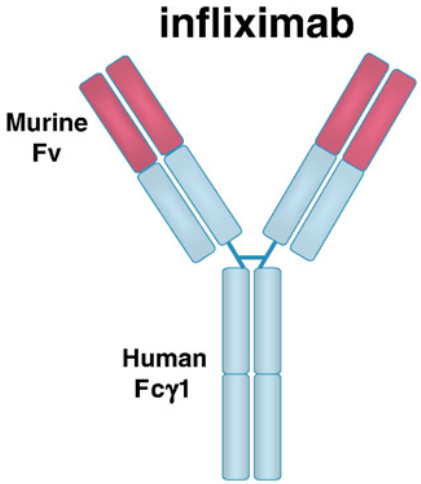
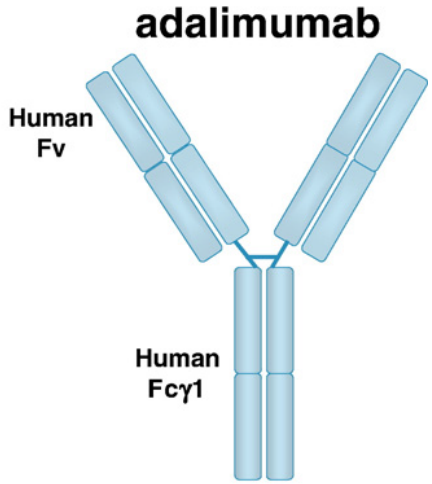


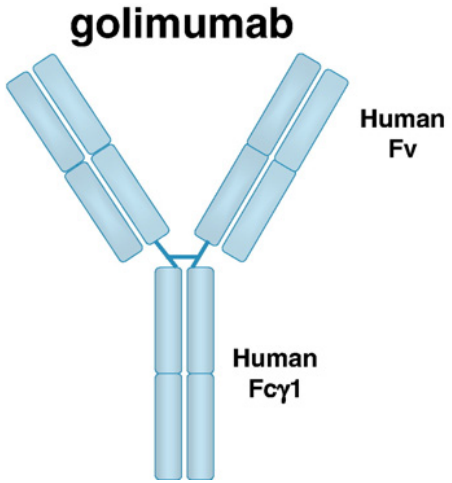
Topics

- Structure
- Immunogenicity
- MoA
- Clinical indications
- Safety
- Specific clinical settings
- Final considerations

Structure

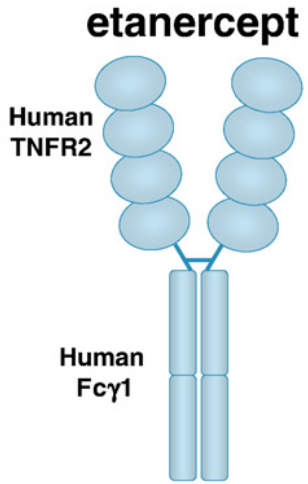






Pharmacology & Therapeutics 117 (2008) 244 – 279

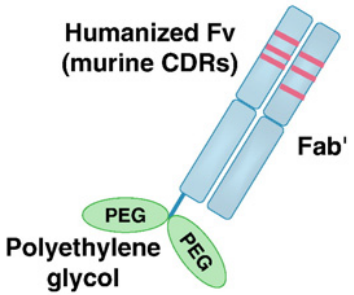
Structure



Pharmacology & Therapeutics 117 (2008) 244 – 279

Structure

certolizumab pegol



Pharmacology & Therapeutics 117 (2008) 244 – 279

Pegylation of Biological Molecules and Potential Benefits: Pharmacological Properties of Certolizumab Pegol

BioDrugs (2014) 28 (Suppl 1):S15–S23

Properties	Effect of Pegylation
Solubility	+
Aggregation	-
Bioavailability	+
Resistance to proteolysis	+
Localisation at disease sites	+
Immunogenicity	-
Circulating half-life	+

Pegylation of Biological Molecules and Potential Benefits: Pharmacological Properties of Certolizumab Pegol

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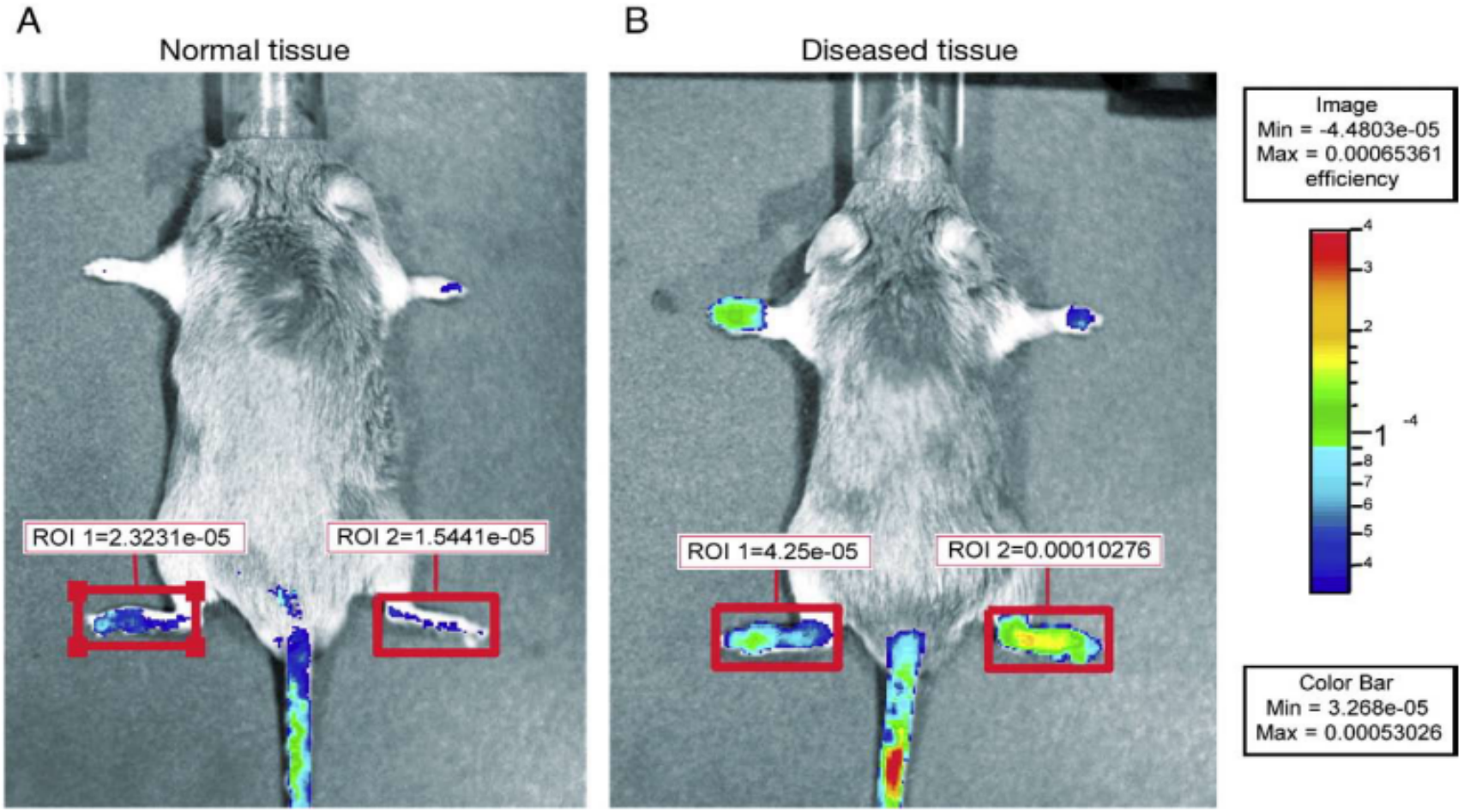
Circulating half-life	+

Use of biofluorescence imaging to compare the distribution of certolizumab pegol, adalimumab, and infliximab in the inflamed paws of mice with collagen-induced arthritis

Journal of Immunological Methods 348 (2009) 36–41

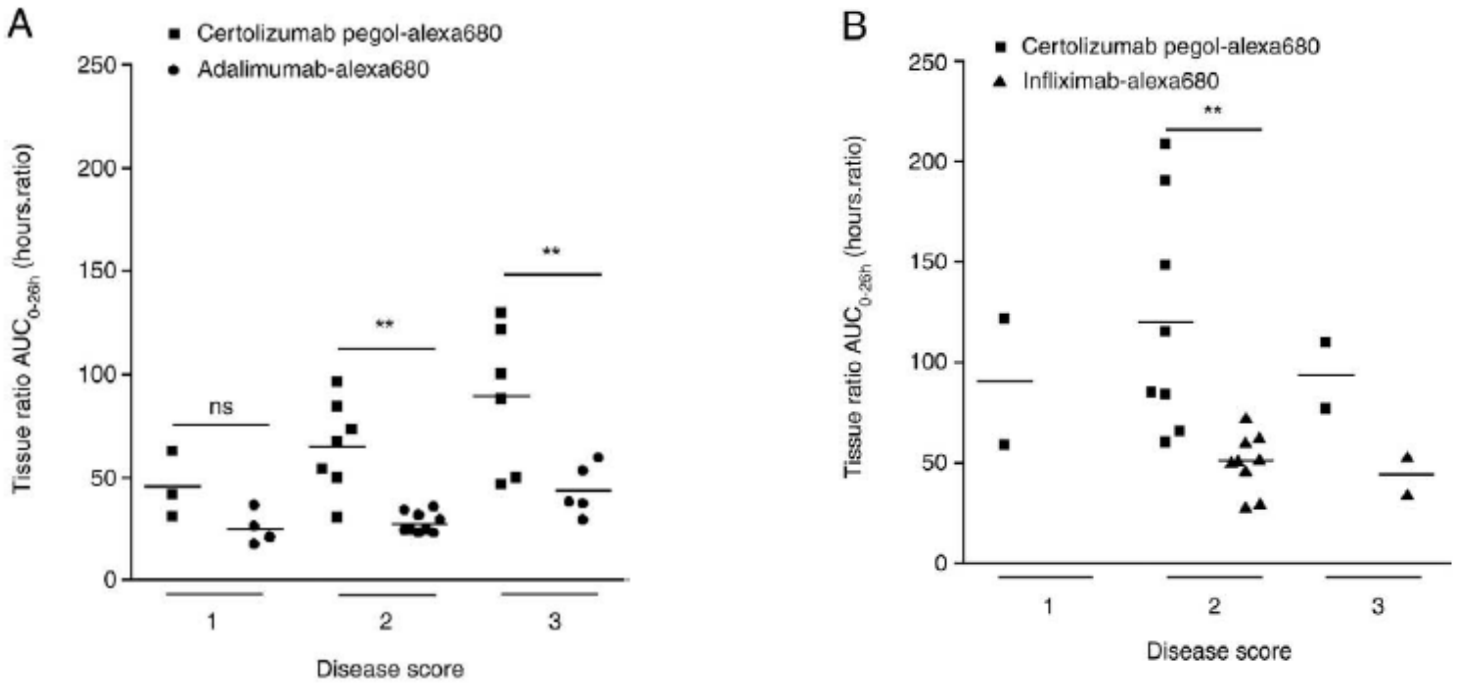
AIM: to determine drug (TNFi) distribution through in vivo-murin model of collagen induced arthritis using a biofluorescence method.



Use of biofluorescence imaging to compare the distribution of certolizumab pegol, adalimumab, and infliximab in the inflamed paws of mice with collagen-induced arthritis

Journal of Immunological Methods 348 (2009) 36–41

Relationship between disease severity score and TNFi accumulation

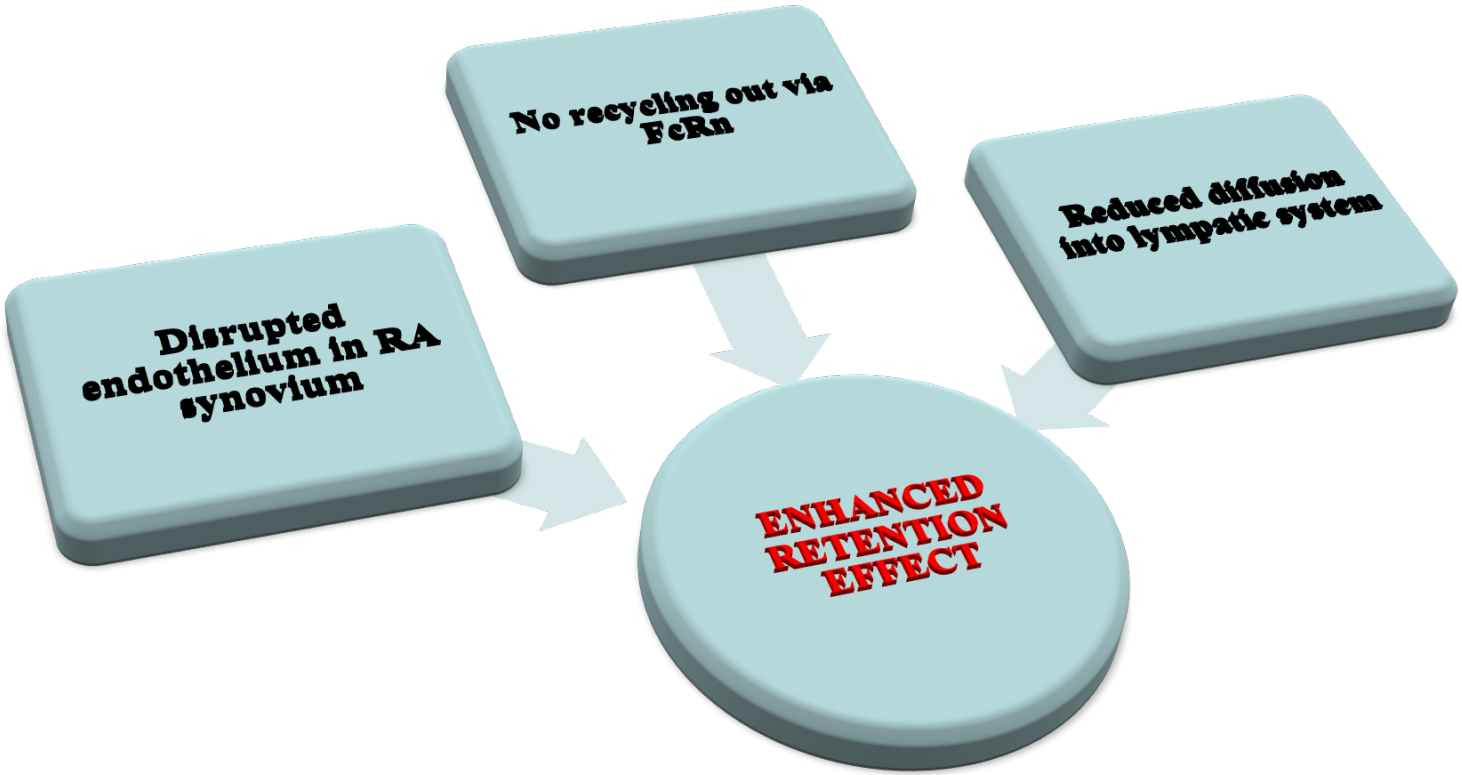


RESULT 3: the degree of CZP penetration in inflamed tissues better agrees with the level of inflammation

Use of biofluorescence imaging to compare the distribution of certolizumab pegol, adalimumab, and infliximab in the inflamed paws of mice with collagen-induced arthritis

Journal of Immunological Methods 348 (2009) 36–41

Thanks to Pegylation



Pegylation of Biological Molecules and Potential Benefits: Pharmacological Properties of Certolizumab Pegol

BioDrugs (2014) 28 (Suppl 1):S15–S23

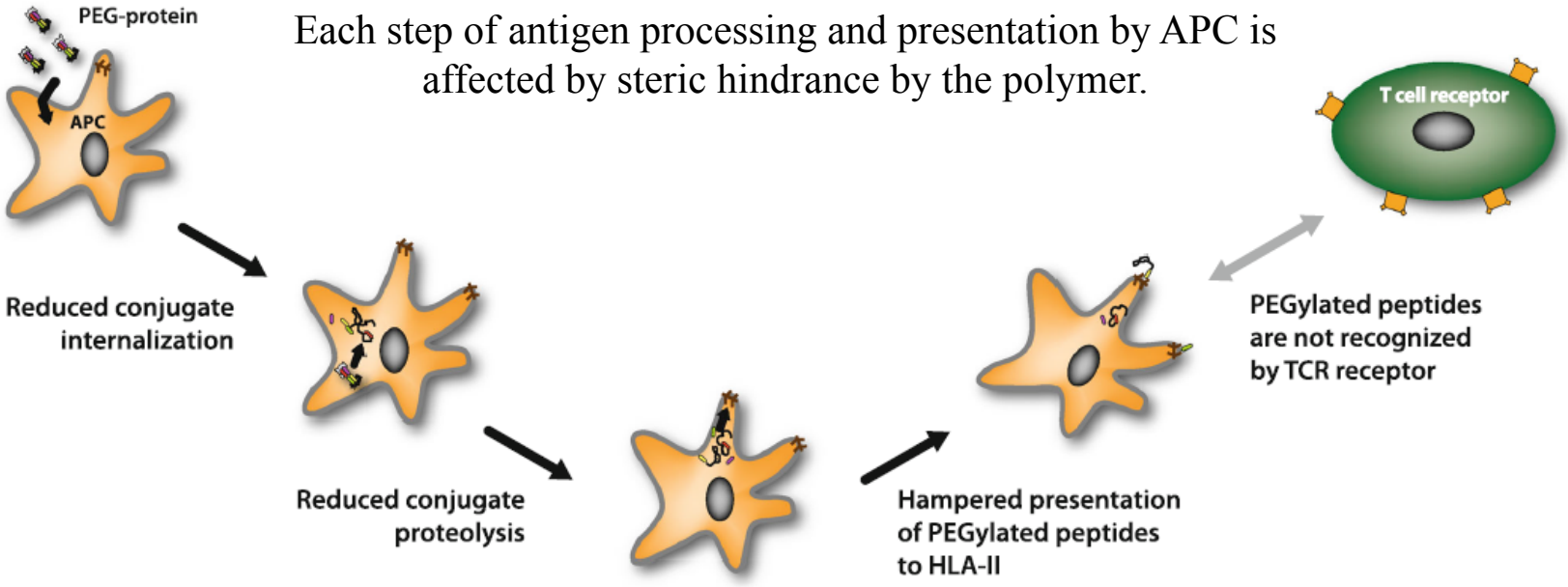
Properties	Effect of Pegylation
Solubility	+
Aggregation	-
Bioavailability	+
Resistance to proteolysis	+
Localisation at disease sites	+
Immunogenicity	**-**
Circulating half-life	+

Pegylation of Biological Molecules and Potential Benefits: Pharmacological Properties of Certolizumab Pegol

BioDrugs (2014) 28 (Suppl 1):S15–S23

PEGylation leads to
reduced immunogenicity, as consequence of the decreased recognition of PEGylated proteins by the immune system.

Each step of antigen processing and presentation by APC is affected by steric hindrance by the polymer.



Pegylation of Biological Molecules and Potential Benefits: Pharmacological Properties of Certolizumab Pegol

BioDrugs (2014) 28 (Suppl 1):S15–S23

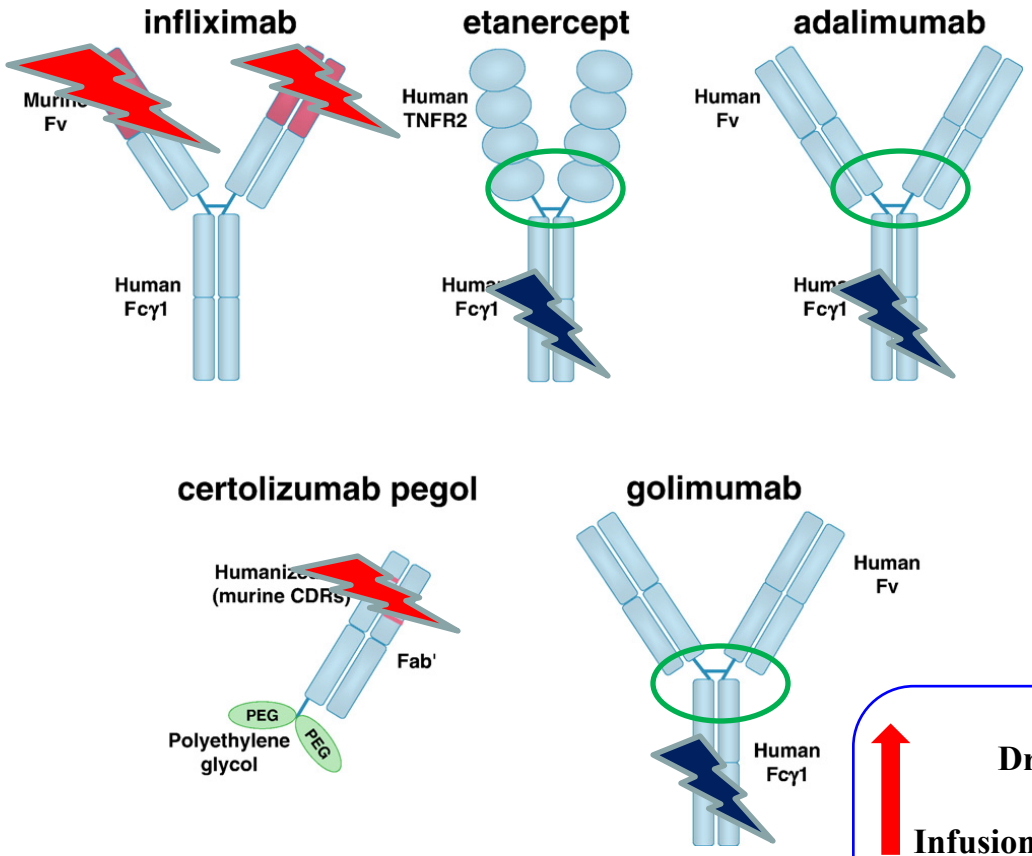
- PEG is approved by the US FDA as a safe constituent of various medications for internal or external use.

- There are minimal safety concerns regarding the linking of PEG to a biological molecule or protein.

Immunogenicity

Anti-drug antibodies (ADAs)

- Non human parts
- Non-self Ig
- Neo-epitopes



- Drug clearence
- Infusion/injection reaction
- Clinical efficacy

Immunogenicity

Variability in ANTI-DRUG ANTIBODIES (ADAs):

- intrinsic immunogenicity of the drug (CZP!)

- individual patients'factors

- concomitant immunosuppression

- assay tests (false + related to RF+)

Immunogenicity

Table 2. Effect of Concomitant Use of Immunomodulators on the Pharmacokinetics and Immunogenicity of Anti-TNFα Biologic Therapies in Patients with Rheumatoid Arthritis or Crohn's Disease

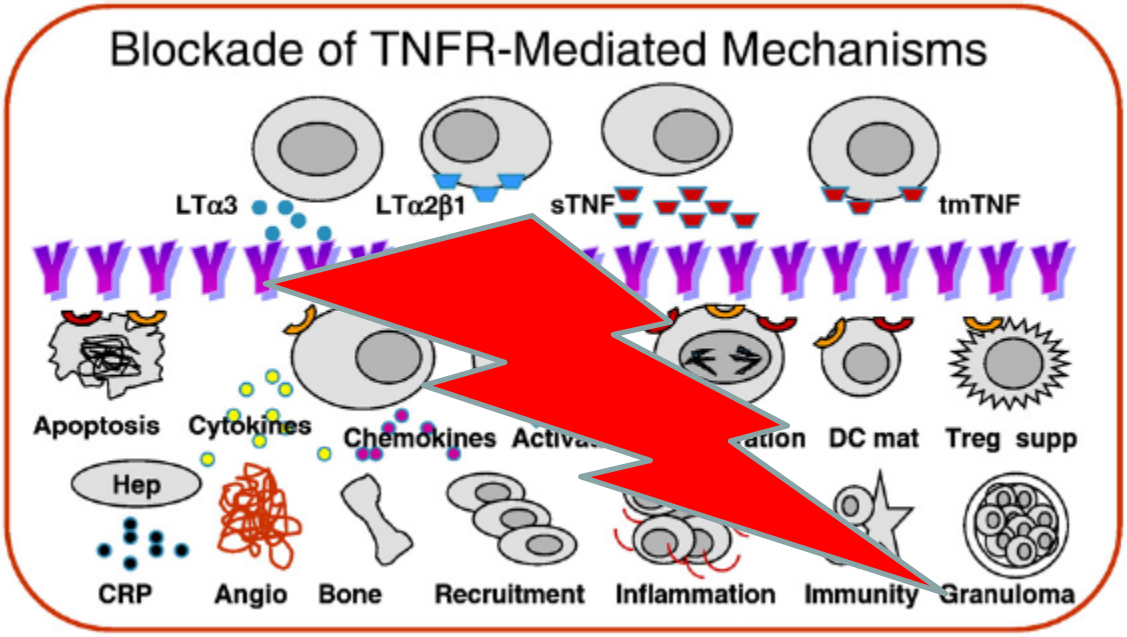
	Disease population	IMM use	Effect on PK	Effect of IMM on ADA Incidence: IM−	Effect of IMM on ADA Incidence: IM+	References
Adalimumab	RA	MTX	MTX reduced the apparent CL of adalimumab in patients with RA after single and repeated dosing by 29% and 44%, respectively.	12% 38%	1% 12%	13, 45
	CD	AZA, 6-MP and MTX	Concurrent immunosuppressant therapy did not appear to affect the apparent CL of adalimumab in patients with CD.	4%	0%	24, 91
Certolizumab pegol	RA	MTX	MTX did not appear to have an effect on the apparent CL of certolizumab in patients with RA.	8%	2%	42
	CD	AZA, 6-MP and MTX	Concurrent immunosuppressant therapy had a small effect on the CL of certolizumab in patients with CD.	11%	3%	42
Etanercept	RA	MTX	MTX did not affect the apparent CL of etanercept in patients with RA.	3%	<2%	21, 43, 92, 93
Golimumab	RA	MTX	MTX reduced the apparent CL of golimumab by 36% after 6-month treatment in patients with RA.	7%	2%	18, 41
Infliximab	RA	MTX	MTX decreased infliximab CL by 30% in patients with RA.	7–53%	0–15%	40, 94
	CD	AZA, 6-MP and MTX	Concurrent IMM use was associated with a 14% decrease in infliximab CL.	11% 15%	7% 1%	26, 27, 95

The Journal of Clinical Pharmacology
2015 55(S3) S60–S74

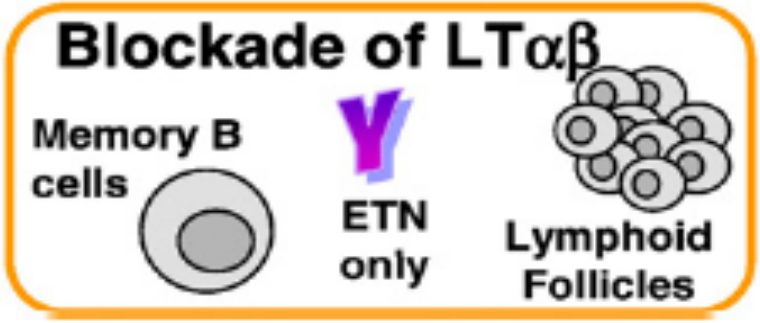
TNFi

MoA

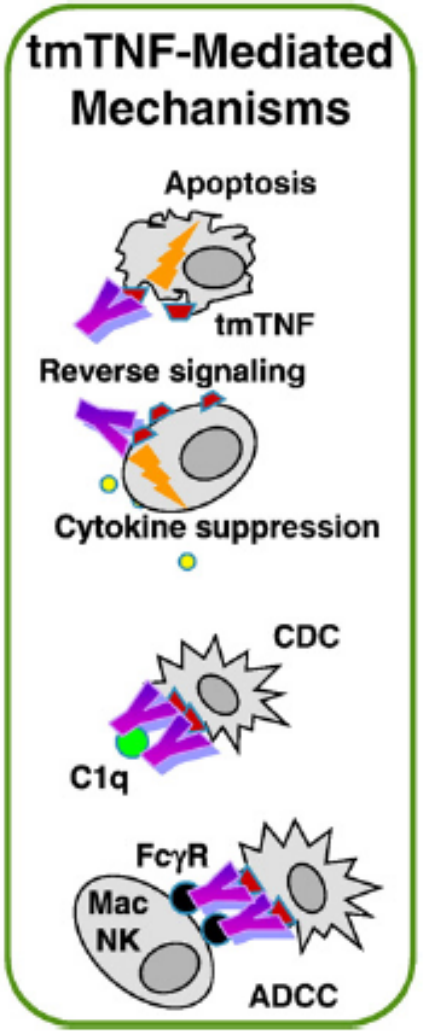
ALL TNFi



ONLY ETA



MAINLY mABs (< ETA)



MoA

Summary of in vitro properties of TNFi

DRUG	INDUCTION OF APOPTOSIS	INDUCTION OF CDC/ADCC	NEUTROPHIL DEATH/ DEGRANULATION	CYTOKINE SUPPRESSION
CZP	-	-	-	+
ETA	+/-	+/-	+/-	+
ADA	+	+	+	+
IFX	+	+	+	+
GOL	+	+	+	+

BioDrugs (2014) 28 (Suppl 1):S5–S13

Pharmacokinetics

	Administration route	Dosage	Half-life	Volume of distribution
ETANERCEPT	SC	25 mg BWK 50 mg BWK	4 days	8 L
ADALIMUMAB	SC	40 mg EOW	10/20 days	4,7-6 L
INFLIXIMAB	IV	3/10 mg/Kg 4-8 weeks	8/10 days	4,3+/2,5 L
GOLIMUMAB	SC	50/100 mg q4w	7/20 days	6,9 L
CZP	SC	200/400 mg Q2w or 4qw	14 days	8 L

Pharmacology & Therapeutics 117 (2008) 244–279

Clinical indications

	RA	PsA	AS	nr-axial SpA	Enteso-arthritis	CD	UC	Uveitis	Hidrosadenitis suppurativa
ETA	+	+	+	+	-	-	-	-	-
ADA	+	+	+	+	+	+	+	+	+
IFX	+	+	+	-	-	+	+	-	-
GOL	+	+	+	+	-	-	+	-	-
CZP	+	+	+	+	-	-	-	-	-

Clinical indications

	RA	MTX required (label indication)	MTX naive	MTX experienced	TNF IR
ETA	+	+/	+	+	+
ADA	+	+/	+	+	+
IFX	+	+	+	+	+
GOL	+	+	+	+	+
CZP	+	+/	+	+	+

TNFis in early naive RA

Study, year	Drug	Population	Endopoints	Results
Quinn MA, 2005	**IFX**	csDMARD naive Early (<1 year) Aggressive disease (PISA score)	ACR20 at 14 weeks ACR50 at 1 year	60% in IFX+MTX 80% in IFX+MTX
PREMIER, 2006	**ADA**	csDMARD naive Early (<3 years) Aggressive disease	ACR50 at 1 year	62% in ADA+MTX
GO-BEFORE, 2011	**GOL**	csDMARD naive Early (< 3 years) active disease	ACR50 at 24 weeks	39% in GOL (combined)+MTX
COMET, 2008	**ETA**	csDMARDs naive Early (< 2 years) active disease	ACR50 at 1 year	71% in ETA50+MTX
C-EARLY, 2016	**CZP**	csDMARDs naive Early (< 1 year) active poor prognosis	ACR50 at 1 year	62% in CZP+MTX

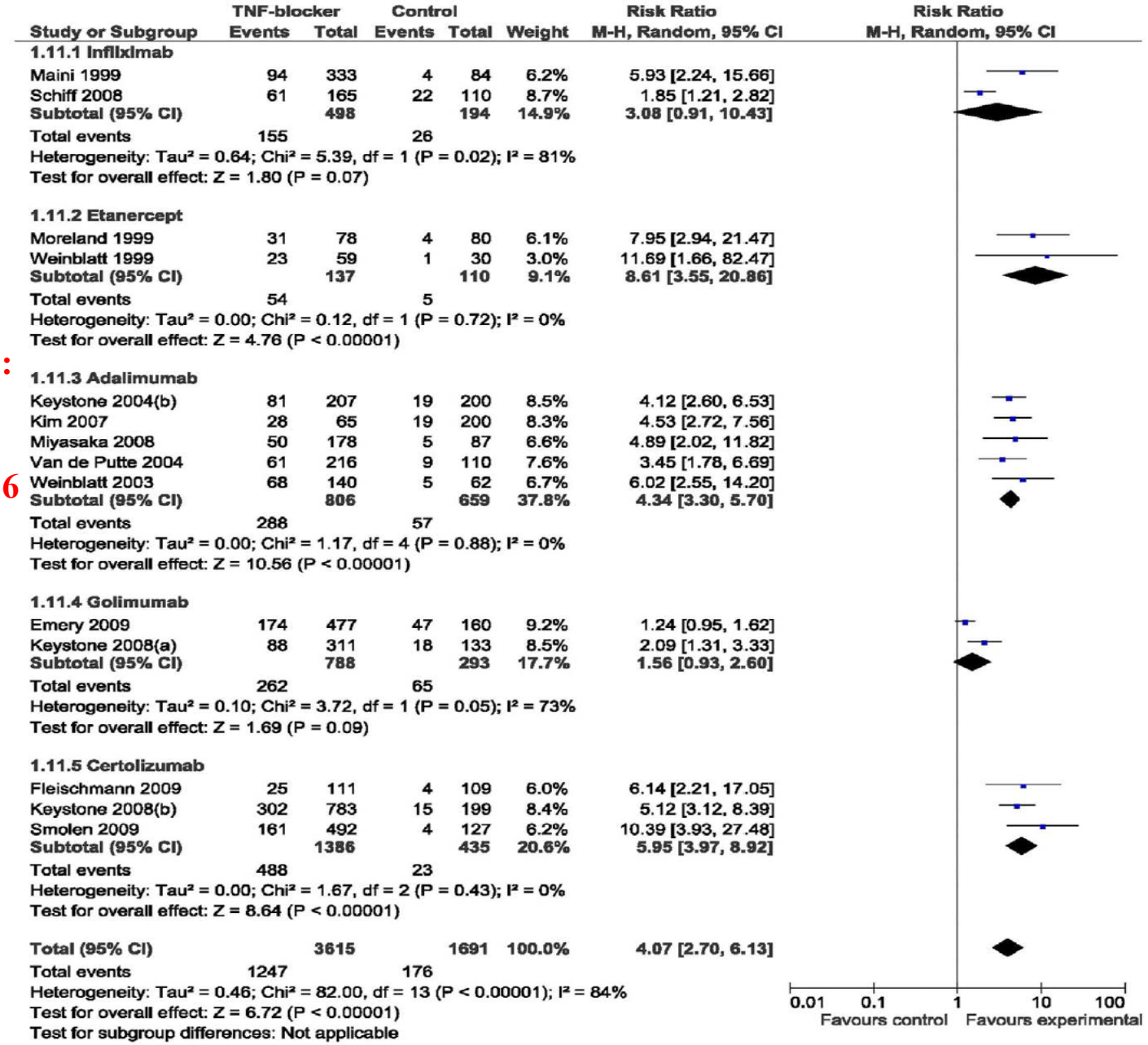
TNFis in MTX-IR RA

Anti-TNFα agent	Disease Population	Efficacy	Treatment group (A) MTX monotherapy	(B) Anti-TNFα monotherapy	(C) MTX + Anti-TNFα	*P*-Value	References
Adalimumab	MTX-inadequate response	ACR20 at Week 24	30%	NS	63%	≤0.001	22
		ACR20 at Week 52	24%	NS	59%	≤0.001	
		ACR50 at Week 24	10%	NS	39%	≤0.001	
		ACR50 at Week 52	10%	NS	42%	≤0.001	
		Mean change in Sharp score through Week 52	2.7	NS	6.1	≤0.001	
	MTX-naive	ACR20 at Week 52	63%	54%	73%	<0.001 (C vs B) =0.022 (C vs A)	23
		ACR50 at Week 52	46%	41%	62%	<0.001 (C vs B) <0.001 (C vs A)	
		Mean change in sharp score through week 52	5.7	3.0	1.3	=0.002 (C vs B) <0.001 (C vs A)	
Certolizumab pegol	MTX-inadequate response	ACR20 at week 24	14%	NS	59%	<0.001	96
		ACR20 at week 52	13%	NS	53%	<0.001	
		ACR50 at week 24	8%	NS	37%	<0.001	
		ACR50 at week 52	8%	NS	38%	<0.001	
		Mean change in sharp score through week 52	2.8	NS	0.4	<0.001	
Etanercept	MTX-inadequate response	ACR20 at week 24	27%	NS	71%	<0.001	21
		ACR50 at week 24	3%	NS	39%	<0.001	
	DMARDs (other than MTX)-inadequate response	ACR20 at week 52	59%	66%	75%	<0.05 (C vs B) <0.05 (C vs A)	14, 48
		ACR50 at week 52	36%	43%	63%	<0.05 (C vs B) <0.05 (C vs A)	
		Mean change in sharp score through week 52	2.80	0.52	−0.54	<0.05 (C vs B) <0.05 (C vs A)	
Golimumab	MTX-inadequate response	ACR20 at week 24	28%	NS[b]	60%	<0.001	97
		ACR50 at week 24	14%	NS[b]	37%	<0.001	
	MTX-Naive	ACR20 at week 24	49%	NS[b]	62%	=0.028	25, 58
		ACR50 at week 24	29%	NS[b]	40%	=0.038	
		Mean change in sharp score through week 52	1.4	NS[b]	0.7	=0.015	
Infliximab	MTX-inadequate response	ACR20 at week 30	20%	NS	50%	<0.001	10, 20
		ACR20 at week 54	17%	NS	42%	<0.001	
		ACR50 at week 30	5%	NS	27%	<0.001	
		ACR50 at week 54	8%	NS	21%	=0.027	
		Mean change in sharp score through week 54	7.0	NS	1.3	<0.001	
	MTX-Naive	ACR20 at week 54	54%	NS	62%	=0.028	11
		ACR50 at week 54	32%	NS	46%	<0.001	
		Mean change in sharp score through week 54	3.7	NS	0.4	<0.001	

The Journal of Clinical Pharmacology
2015 55(S3) S60–S74

RCTs on MTX-IR PATIENTS:

ACR50 response at 6 months



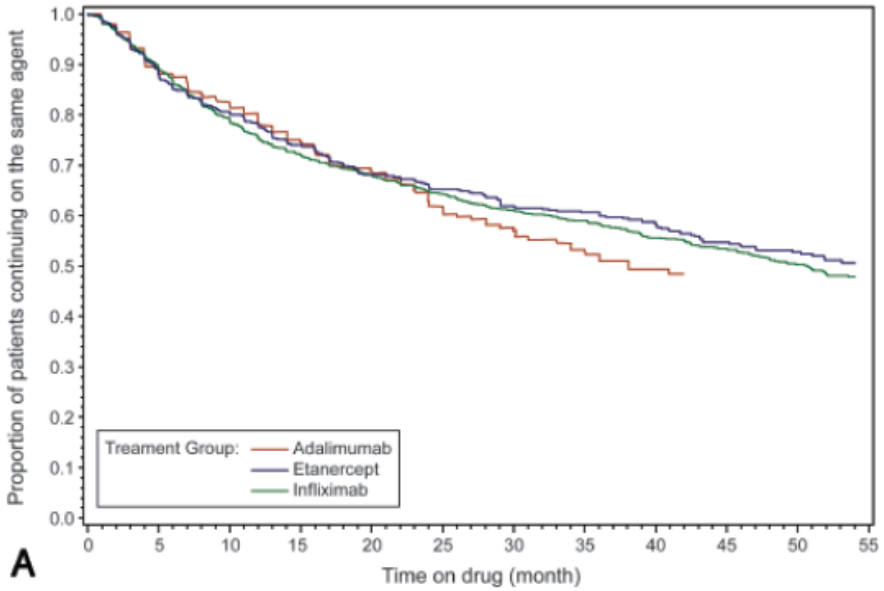
Citation: Aaltonen KJ, Virkki LM, Malmivaara A, Konttinen YT, Nordström DC, et al. (2012) Systematic Review and Meta-Analysis of the Efficacy and Safety of Existing TNF Blocking Agents in Treatment of Rheumatoid Arthritis. PLoS ONE 7(1): e30275. doi:10.1371/journal.pone.0030275

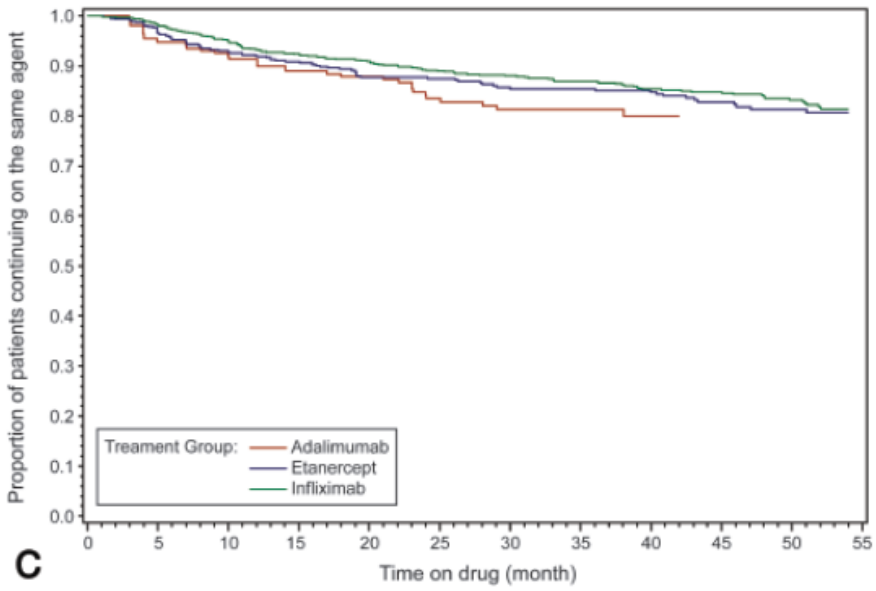
Persistence with Anti-Tumor Necrosis Factor Therapies in Patients with Rheumatoid Arthritis: Observations from the RADIUS Registry

J Rheumatol 2011;38:1273–81

RLD on MTX-IR PATIENTS

RADIUS1: US register, including 2418 RA patients, starting their 1° TNFi



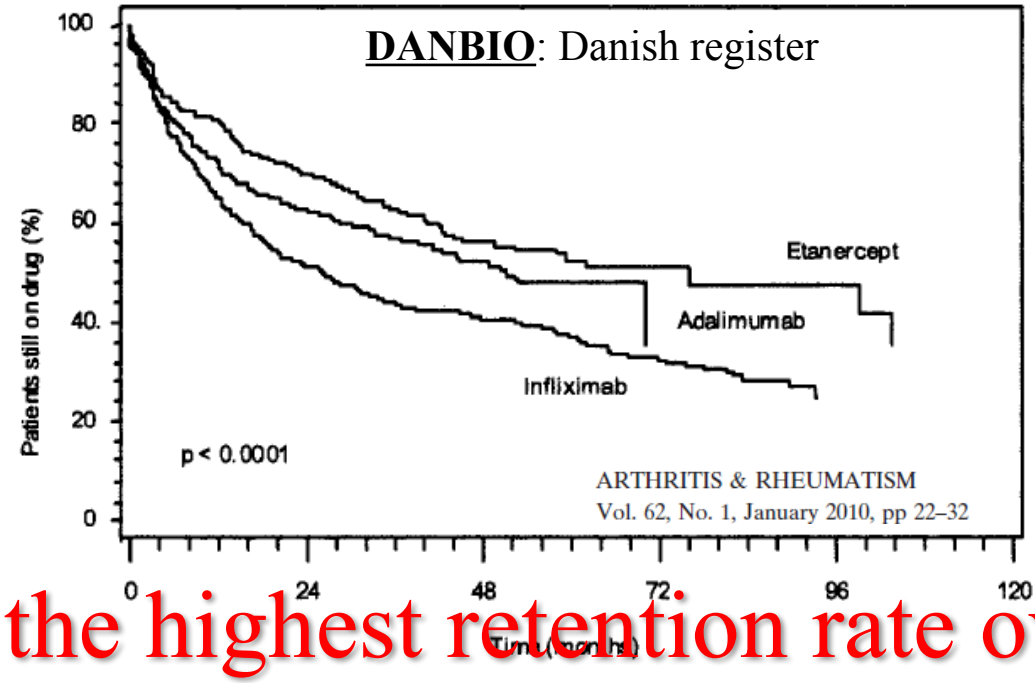


Mean persistence rates were similar among first-course TNFi

Discontinuations of first-course therapy due to ineffectiveness were similar among treatments

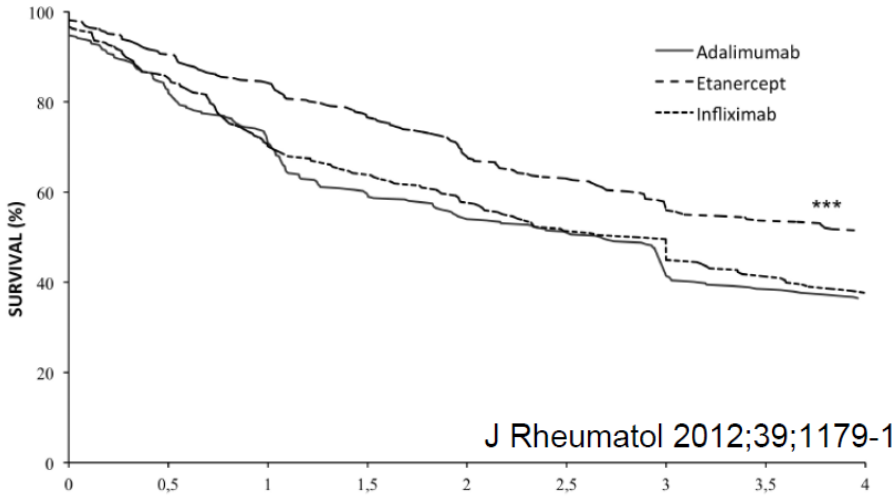
RLD on MTX-IR PATIENTS

DANBIO: Danish register



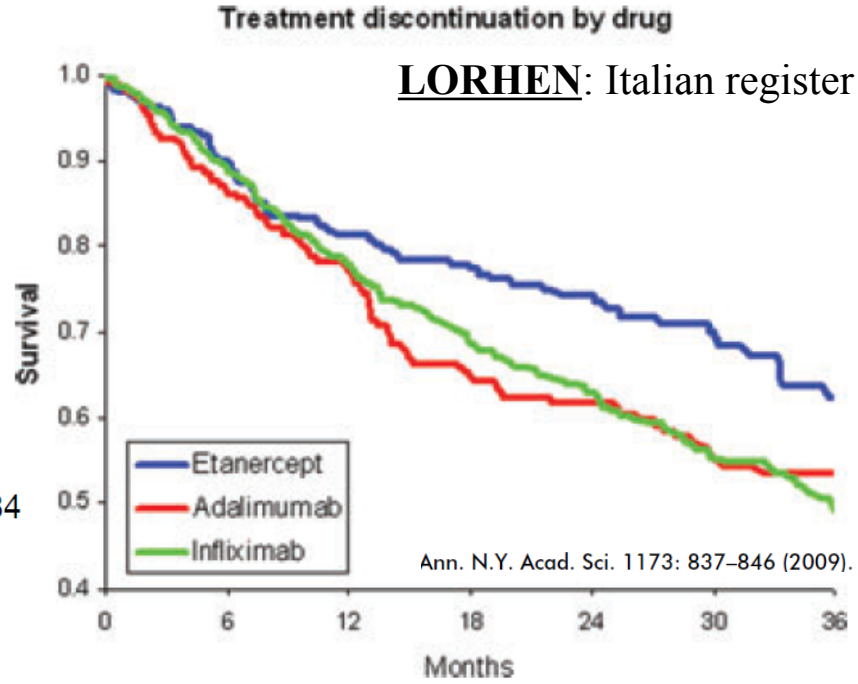
ETA had the highest retention rate over time

GISEA: Italian register



J Rheumatol 2012;39;1179-1184

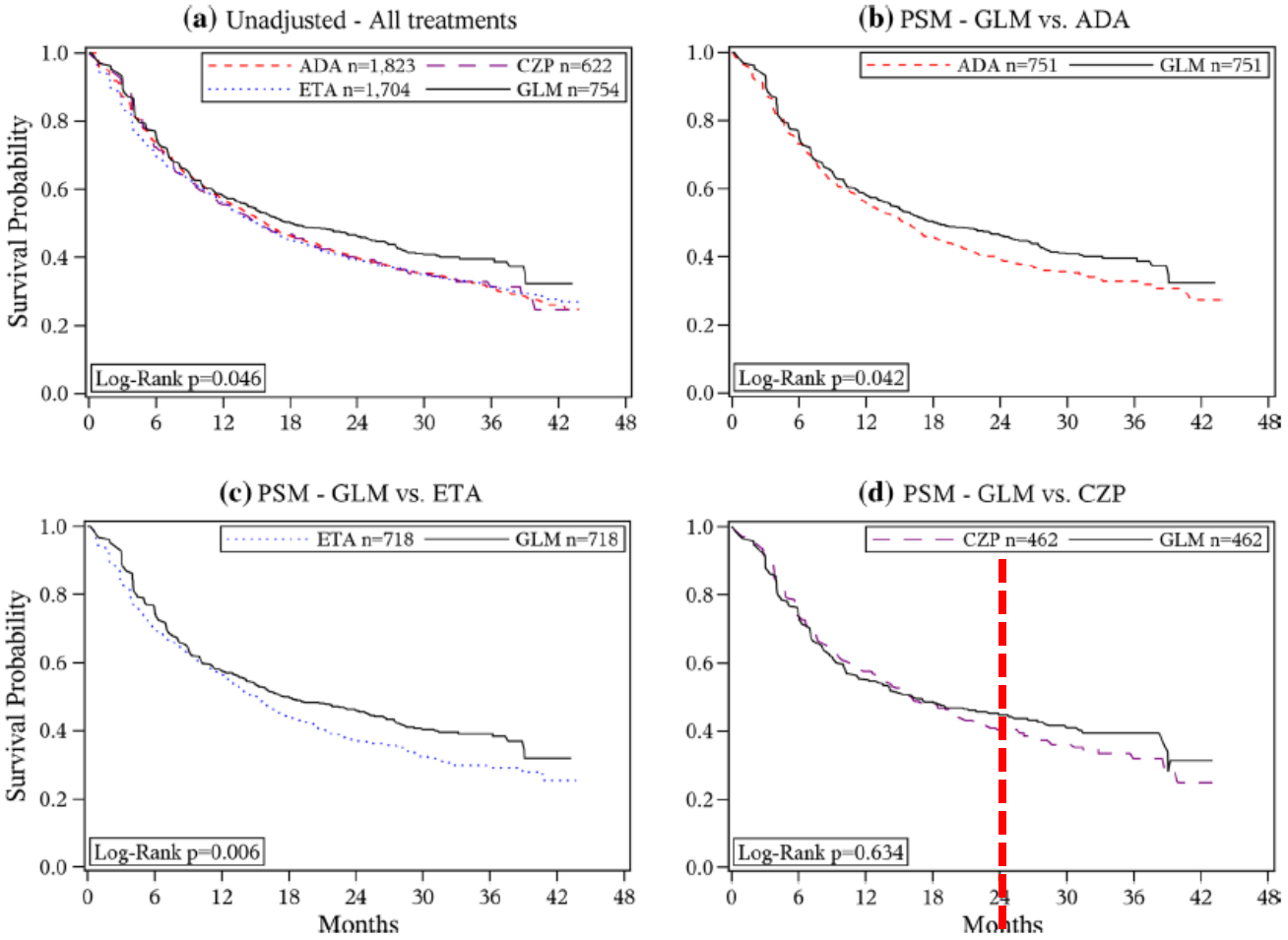
LORHEN: Italian register



Treatment persistence among patients with immune-mediated rheumatic disease newly treated with subcutaneous TNF-alpha inhibitors and costs associated with non-persistence

Rheumatol Int (2016) 36:987–995

Retrospective analysis on Swedish register among AS, PsA and RA patients



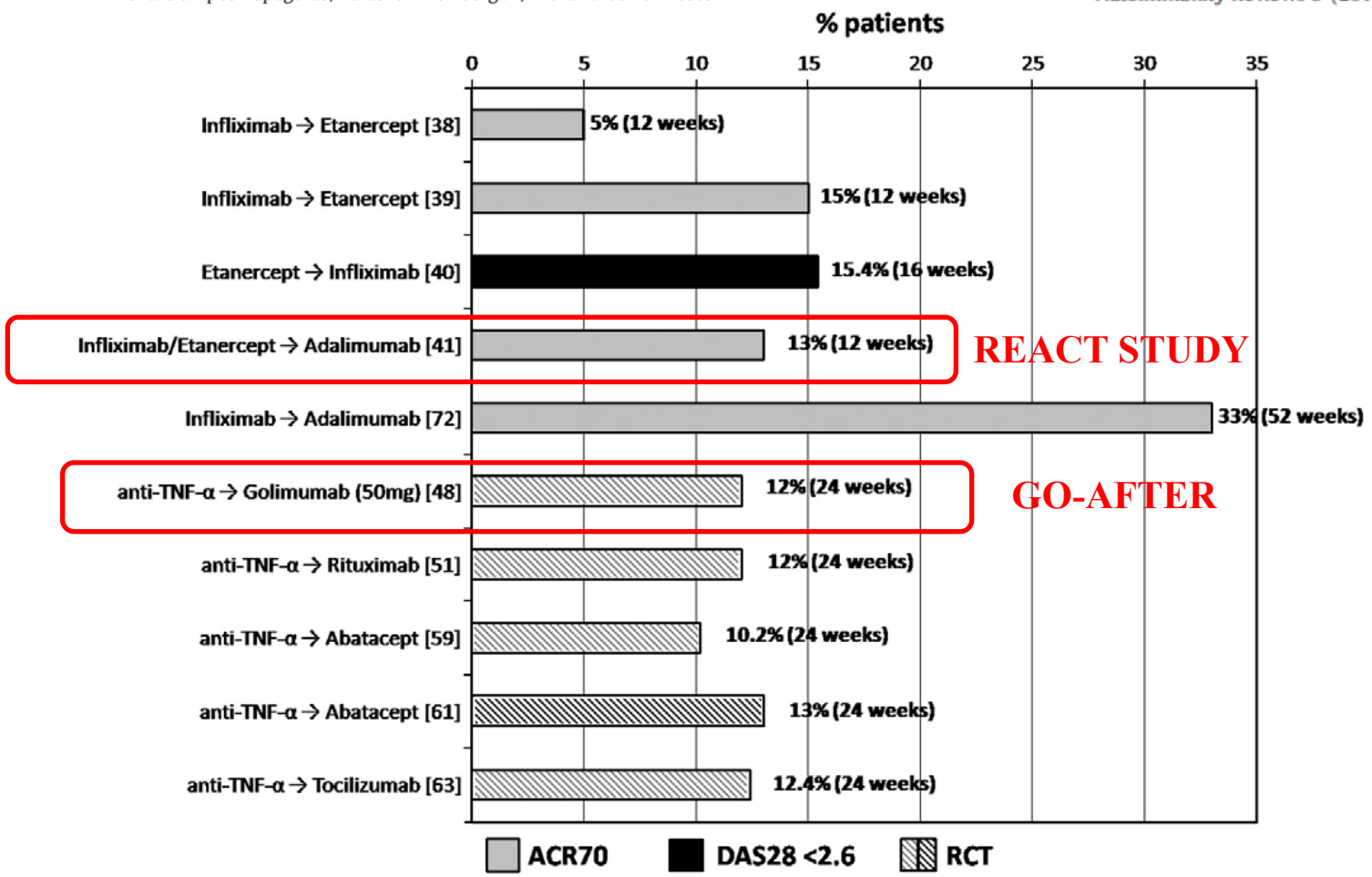
TNFis in TNFi experienced RA

Review

Strategies after the failure of the first anti-tumor necrosis factor α agent in rheumatoid arthritis

Charalampos Papagoras, Paraskevi V. Voulgari, Alexandros A. Drosos *

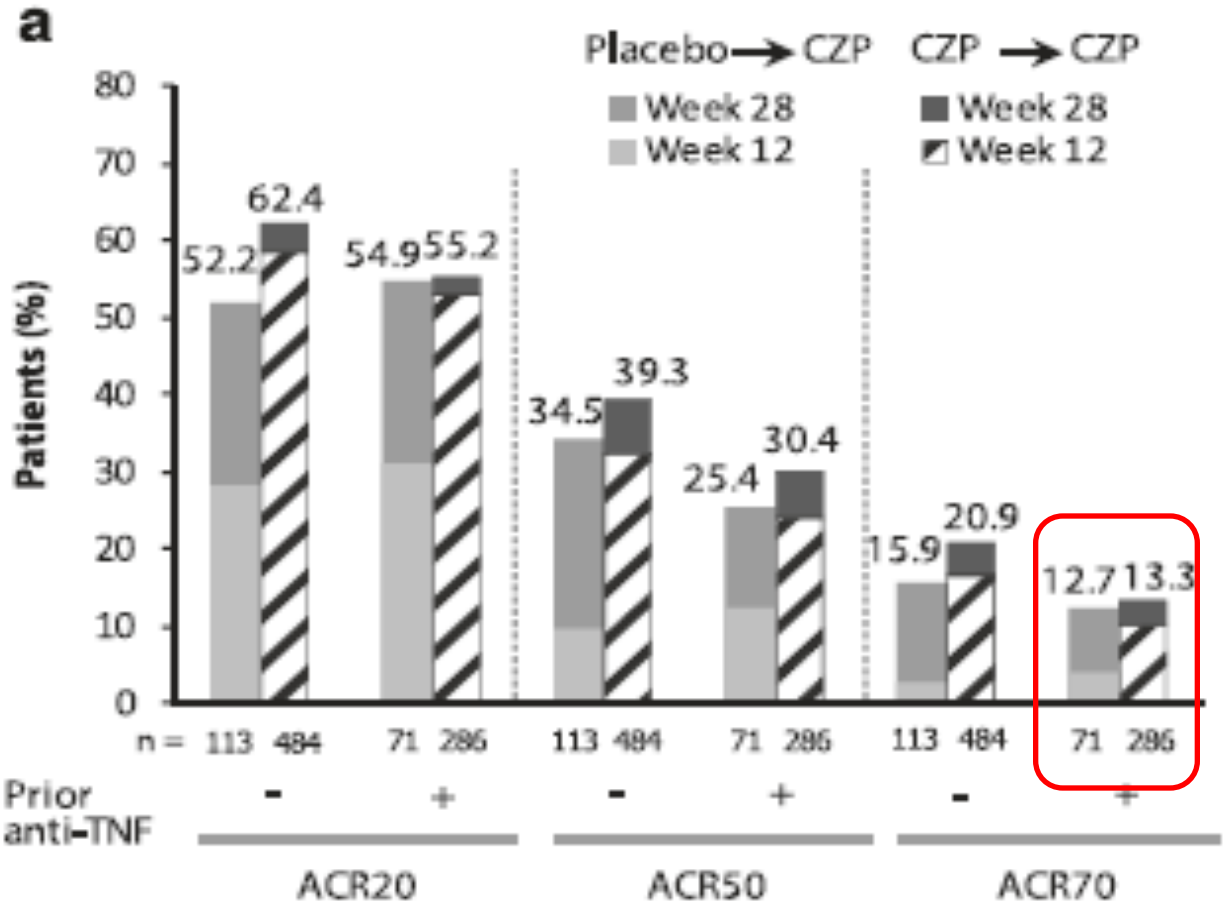
Autoimmunity Reviews 9 (2010) 574–582



Twenty-eight-week results from the REALISTIC phase IIIb randomized trial: efficacy, safety and predictability of response to certolizumab pegol in a diverse rheumatoid arthritis population

Weinblatt *et al. Arthritis Research & Therapy* (2015) 17:325

37% TNFi experienced patients



Might we promptly identify not responding patients to (each) TNFi?

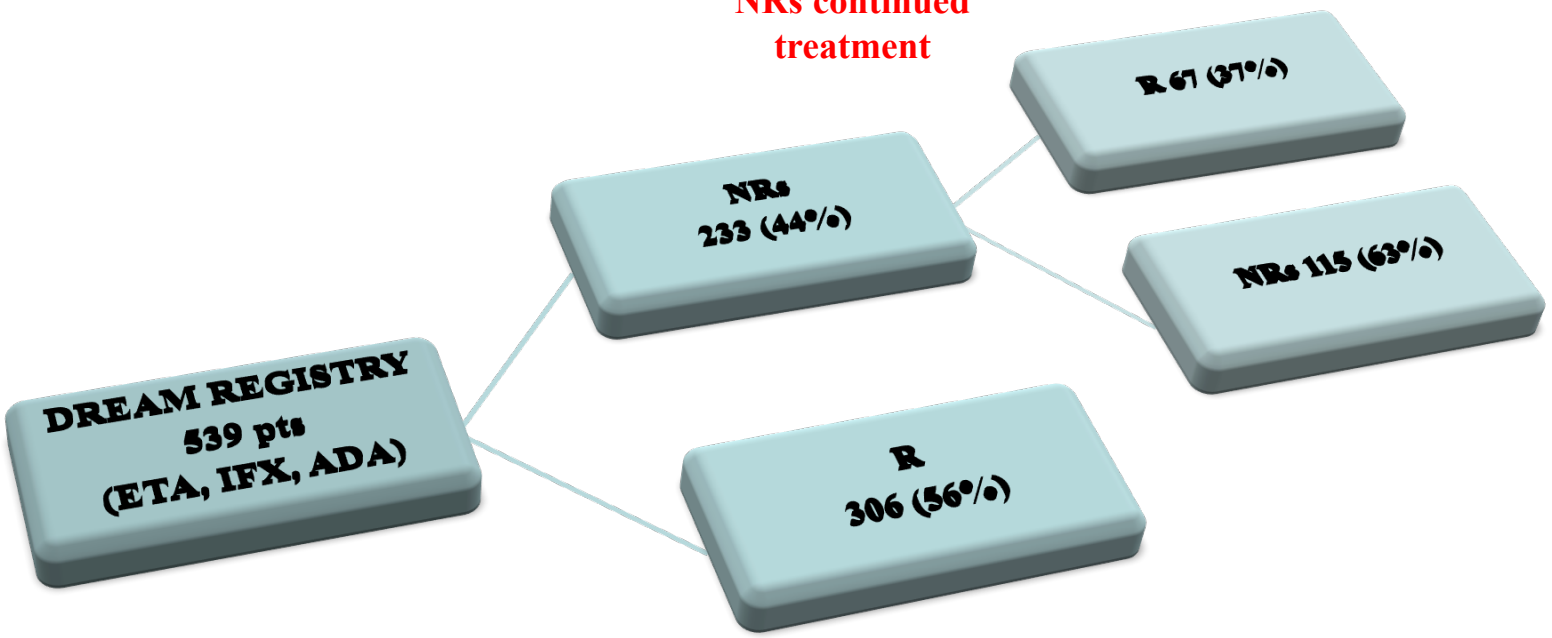
Evaluating guidelines on continuation of anti-tumour necrosis factor treatment after 3 months: clinical effectiveness and costs of observed care and different alternative strategies

Ann Rheum Dis 2009;**68**:844–849.

RESPONDER/R: ΔDAS28>1,2
NON RESPONDER/NR: ΔDAS28≤1,2

37% pts with no response at 3 months, responded at 6 months

81% (189 pts) of NRs continued treatment



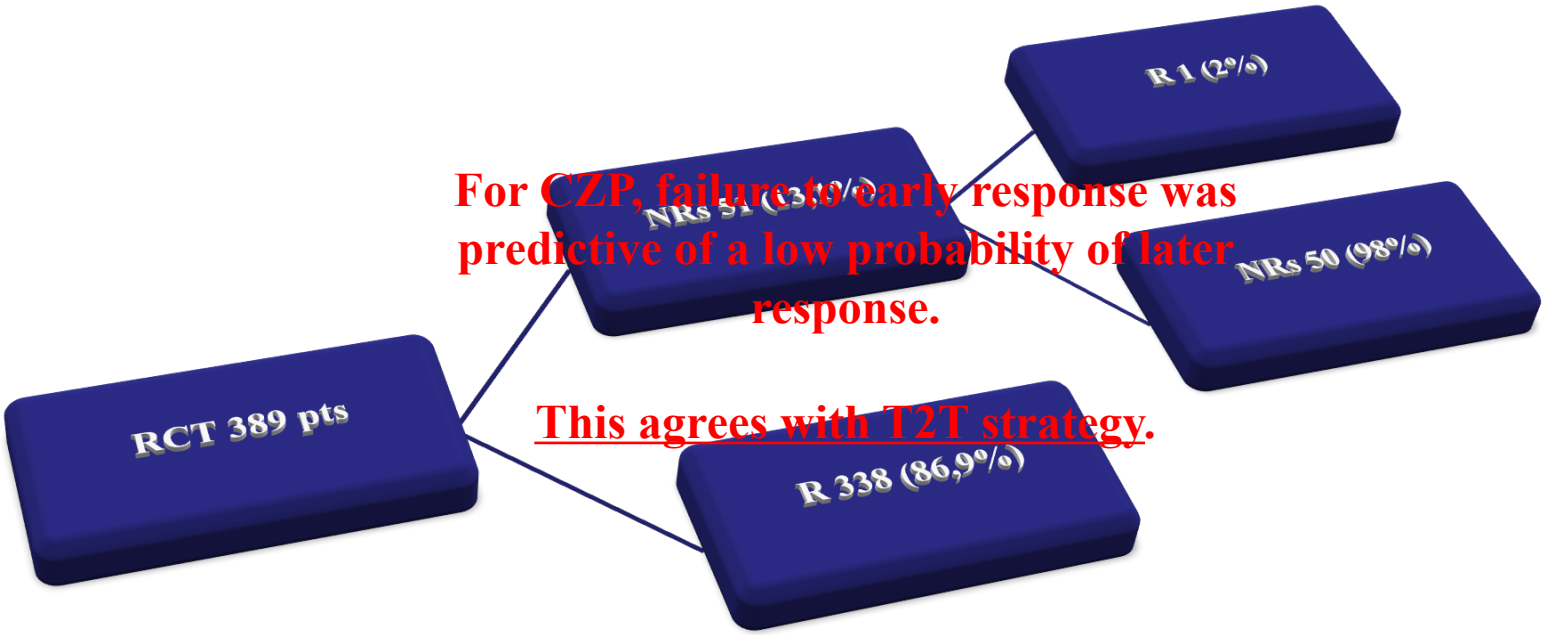
Time (weeks) 0 — 12 weeks — 24 weeks

Timing and Magnitude of Initial Change in Disease Activity Score 28 Predicts the Likelihood of Achieving Low Disease Activity at 1 Year in Rheumatoid Arthritis Patients Treated with Certolizumab Pegol: A Post-hoc Analysis of the RAPID 1 Trial

J Rheumatol 2012;39;1326-1333

RESPONDER/R: ΔDAS28>1,2
NON RESPONDER/NR: ΔDAS28≤1,2

Only 1 pt who did not respond by week 12 went on to achieve LDA at week 52



For CZP, failure to early response was predictive of a low probability of later response.

This agrees with T2T strategy.

Time (weeks) **0** **12 weeks** **52 weeks**

Safety

- RCTs
- Real life data (RLD)

[Overview of Reviews]

Adverse effects of biologics: a network meta-analysis and Cochrane overview

Cochrane Database of Systematic Reviews 2011, Issue 2.

160 RCTs with 48,676 participants and 46 extension studies with 11,954 participants.
The median duration of RCTs was six months and 13 months for OLEs.

Figure 2. Forest plot of network meta-analysis: total adverse events

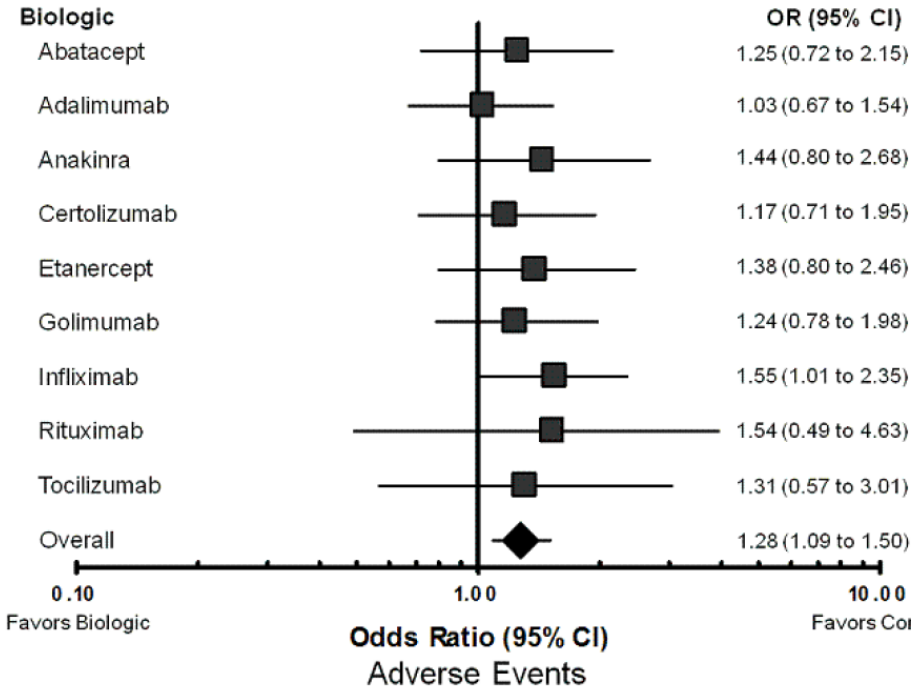
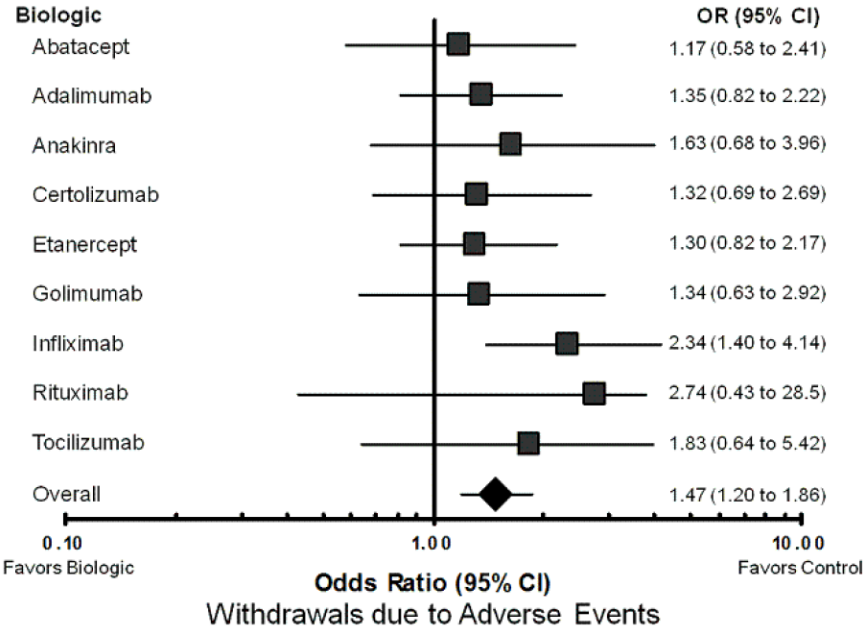


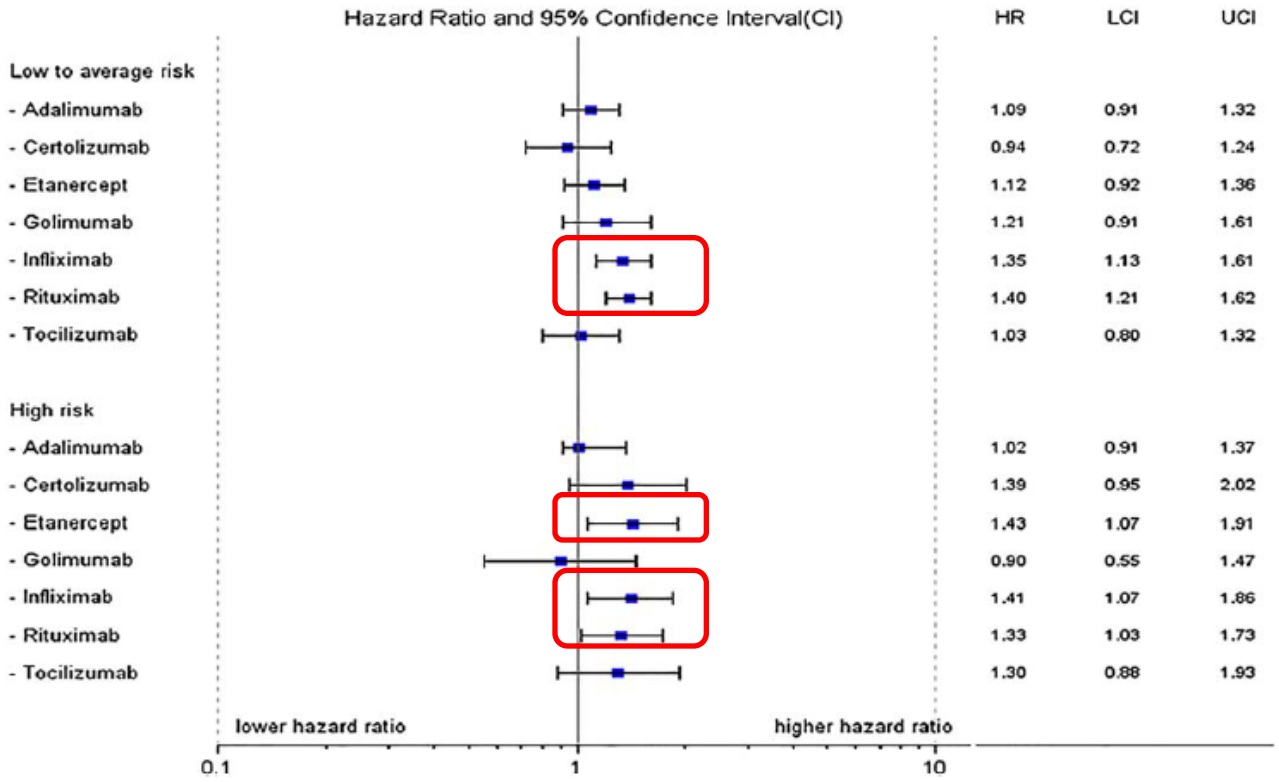
Figure 3. Forest plot of network meta-analysis: withdrawals due to adverse events



Comparative Risk of Hospitalized Infection Associated With Biologic Agents in Rheumatoid Arthritis Patients Enrolled in Medicare

ARTHRITIS & RHEUMATOLOGY
Vol. 68, No. 1, January 2016, pp 56–66

Retrospective analysis of 31,801 new biologic treatment episodes in patients who had previously received another biologic agent.



After adjustment for the infection risk score and other confounders, the risk of hospitalized infection was significantly higher for IFX, ETA and RTX.

Specific clinical setting

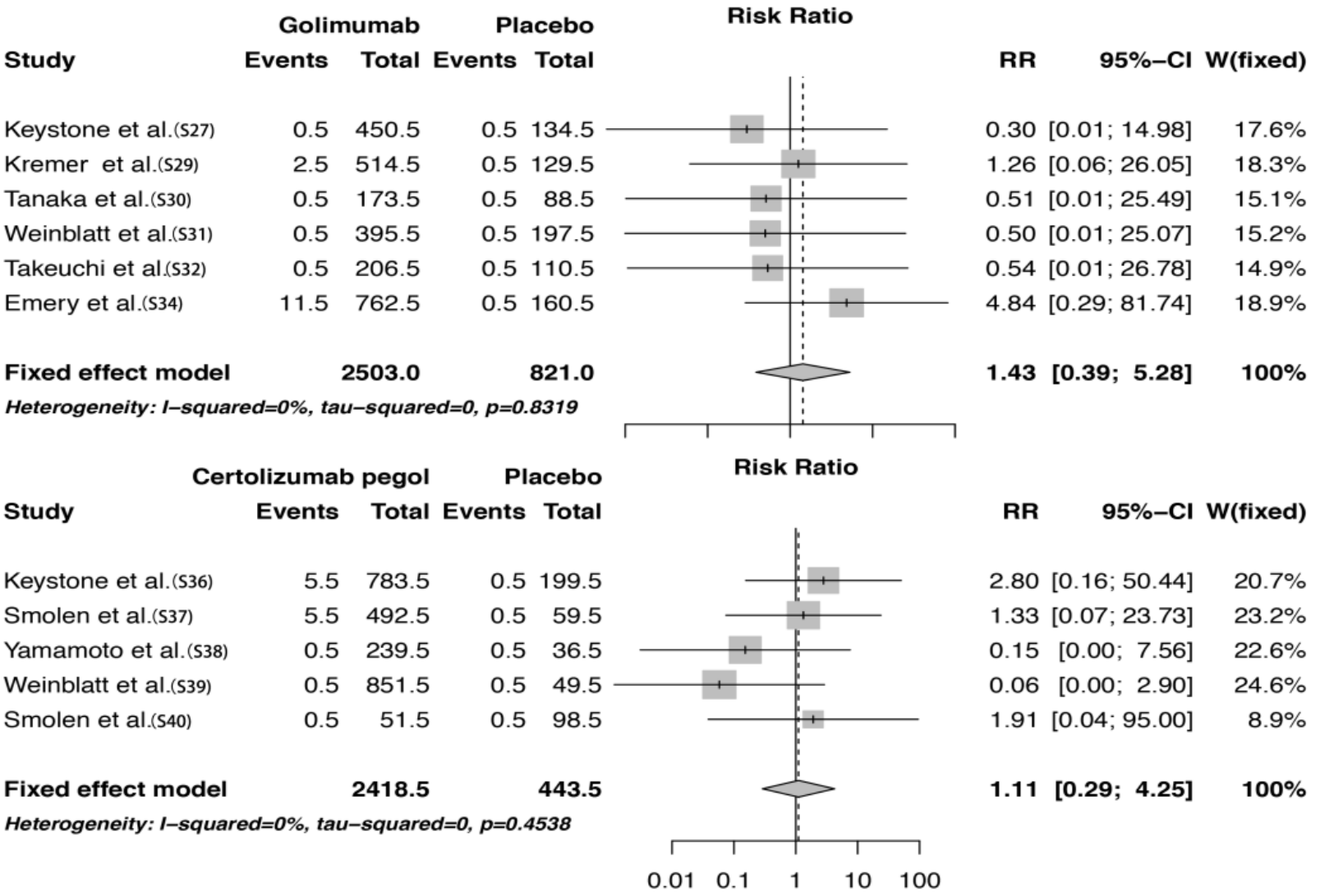
- Latent TBCi
- Pregnancy
- Single site inflammation

The Risk of Tuberculosis in Patients with Rheumatoid Arthritis Treated with Tumor Necrosis Factor- α Antagonist: A Metaanalysis of Both Randomized Controlled Trials and Registry/Cohort Studies

J Rheumatol 2015;42;2229-2237

TBC risk ratio for each TNFi vs placebo in unbiased RCTs

0 cases in 9 RCTs with ETN!

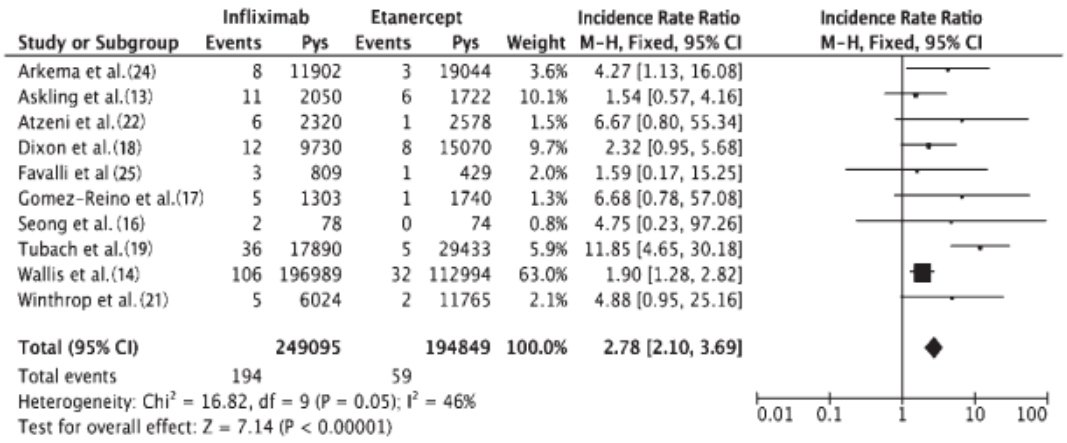


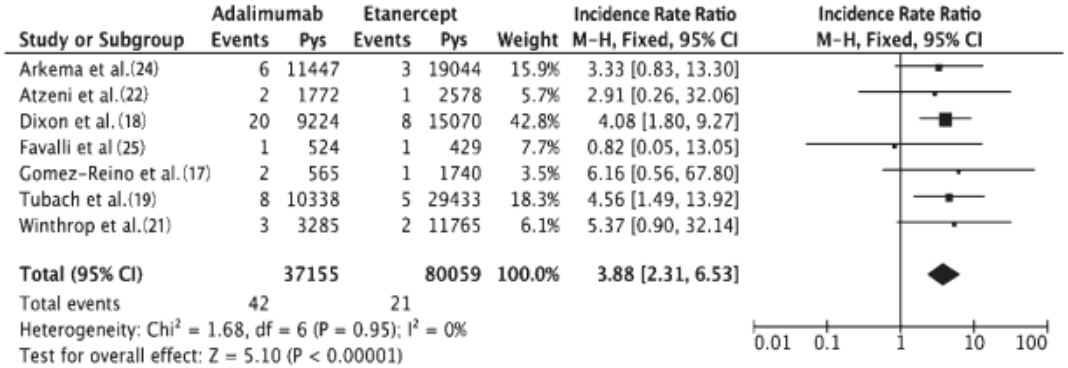
The Risk of Tuberculosis in Patients with Rheumatoid Arthritis Treated with Tumor Necrosis Factor- α Antagonist: A Metaanalysis of Both Randomized Controlled Trials and Registry/Cohort Studies

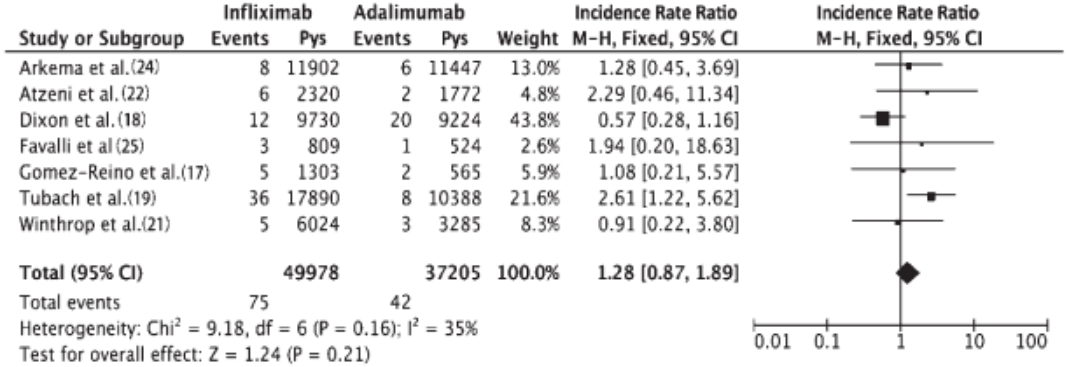
J Rheumatol 2015;42;2229-2237

TBC risk of IFX was 2,78 higher than ETN.

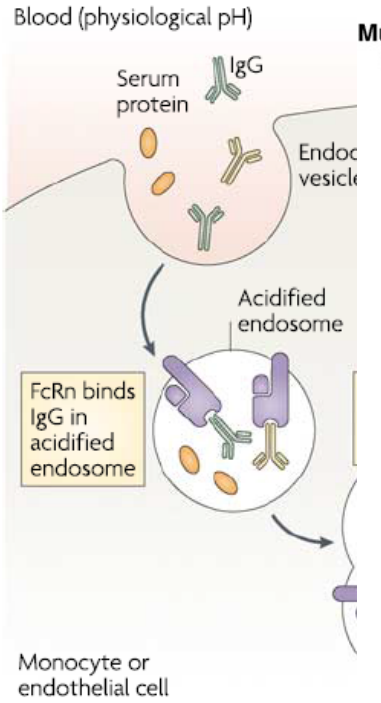
TBC risk of ADA was 3,88 times of ETN, both with statistical significance.

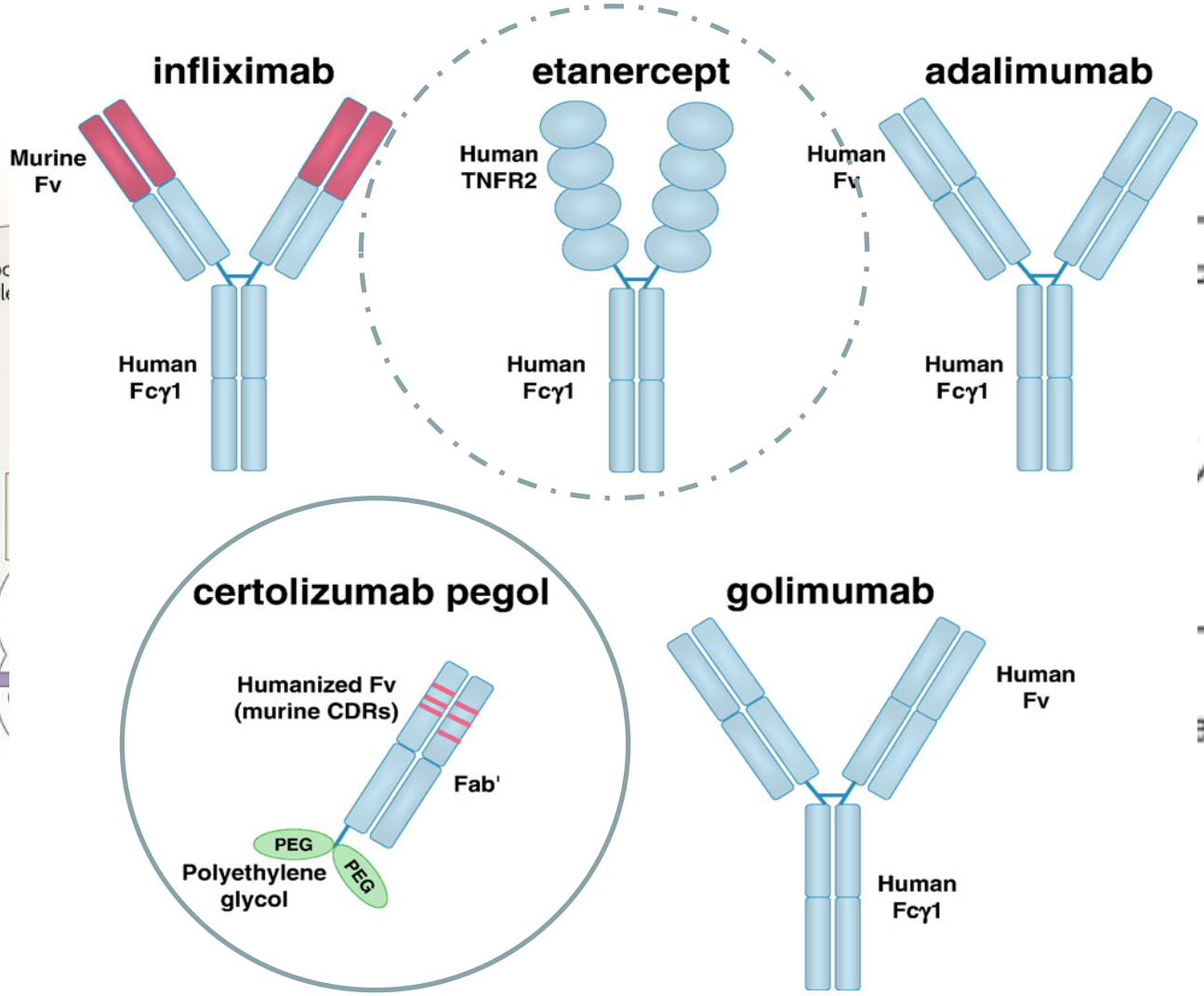


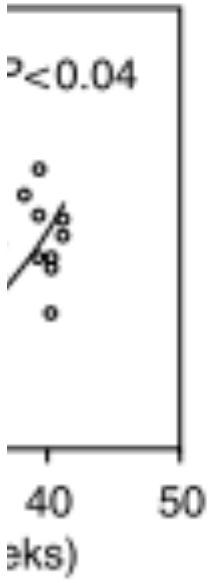




Pregnancy and TNFi







Am J Gastroenterol 2009; 104:228–233

Placental Transfer of Anti-Tumor Necrosis Factor Agents in Pregnant Patients with Inflammatory Bowel Disease

Clin Gastroenterol Hepatol. 2013 March ; 11(3): 286–e24.

	IFX	Range	ADA	Range	CZP	Range
N	11		10		10	
Median Maternal Age (yrs)	36	29-40	32.5	25-40	28	22-42
Disease type (CD:UC)	7:4		8:2		10:0	
Median Disease Duration (years)	10	2-24	11	2-24	6.5	1-10
Concomitant Medications						
• None	6		7		5	
• 5 Aminosalicylates	7		3		2	
• Azathioprine/6MP	3		0		2	
• Prednisone	2		1		3	
Patients exposure to anti-TNF agent by Trimester (n)						
Conception/Trimester 1	11		10		7	
Trimester 2	11		10		9	
Trimester 3	11		10		10	
Post-Partum	11		9		9	
Median Number of drug doses in pregnancy	--		18	14-32	8	3-12

CZP has the lowest level of placental transfer.

Ratio cord/mother (median %) at birth 160% 153% 3,9%

The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation

Götestam Skorpen C, *et al*. *Ann Rheum Dis* 2016;**75**:795–810.

*Points to consider for use of antirheumatic drugs in pregnancy**		Grade of recommendation†
1	csDMARDs‡ proven compatible with pregnancy are hydroxychloroquine, chloroquine, sulfasalazine, azathioprine, ciclosporin, tacrolimus and colchicine. They should be continued in pregnancy for maintenance of remission or treatment of a disease flare.	B
2	csDMARDs‡ methotrexate, mycophenolate mofetil and cyclophosphamide are teratogenic and should be withdrawn before pregnancy.	B
6	Among bDMARDs¶ continuation of tumour necrosis factor (TNF) inhibitors during the first part of pregnancy should be considered. Etanercept and certolizumab may be considered for use throughout pregnancy due to low rate of transplacental passage.	B
7	bDMARDs¶ rituximab, anakinra, tocilizumab, abatacept, belimumab and ustekinumab have limited documentation on safe use in pregnancy and should be replaced before conception by other medication. They should be used during pregnancy only when no other pregnancy-compatible drug can effectively control maternal disease.	D

Among bDMARDs¶ continuation of tumour necrosis factor (TNF) inhibitors during the first part of pregnancy should be considered. Etanercept and certolizumab may be considered for use throughout pregnancy due to low rate of transplacental passage.

BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids

Recommendations for anti-TNF medications in pregnancy and breastfeeding

(i) Infliximab (IFX) may be continued until 16 weeks and etanercept (ETA) and adalimumab (ADA) may be continued until the end of the second trimester (LOE 2−, GOR D, SOA 98.9%).

(ii) To ensure low/no levels of drug in cord blood at delivery, ETA and ADA should be avoided in the third trimester and IFX stopped at 16 weeks. If these drugs are continued later in pregnancy to treat active disease, then live vaccines should be avoided in the infant until 7 months of age (LOE 3, GOR D, SOA 98.9%).

(iii) Certolizumab pegol is compatible with all three trimesters of pregnancy and has reduced placental transfer compared with other TNF inhibitors (TNFis) (LOE 2−, GOR D, SOA 97.9%).

(iv) Golimumab is unlikely to be harmful in the first trimester (LOE 4, GOR D, SOA 97.9%)

(v) Women should not be discouraged from breastfeeding on TNFis, but caution is recommended until further information is available (LOE 3, GOR D, SOA 98.4%).

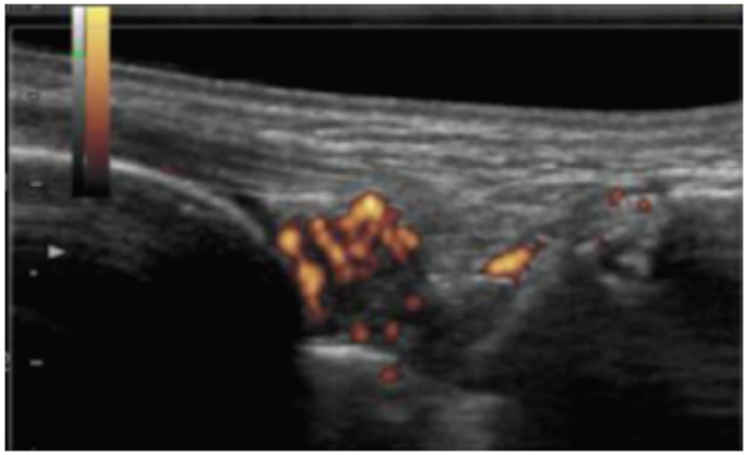
(vi) Based on limited evidence IFX, ETA and ADA are compatible with paternal exposure (LOE 2−, GOR D, SOA 98.9%).

Case Report

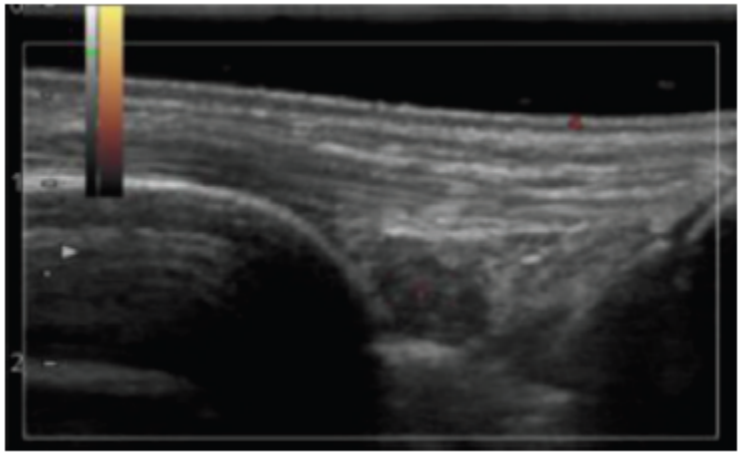
Effectiveness of Certolizumab Pegol in Treating Rheumatoid Arthritis Patients with Persistent Inflamed Residual Mono- or Oligosynovitis Resistant to Prior TNF-α Inhibitors

Case Reports in Rheumatology
Volume 2015, Article ID 348614

Before



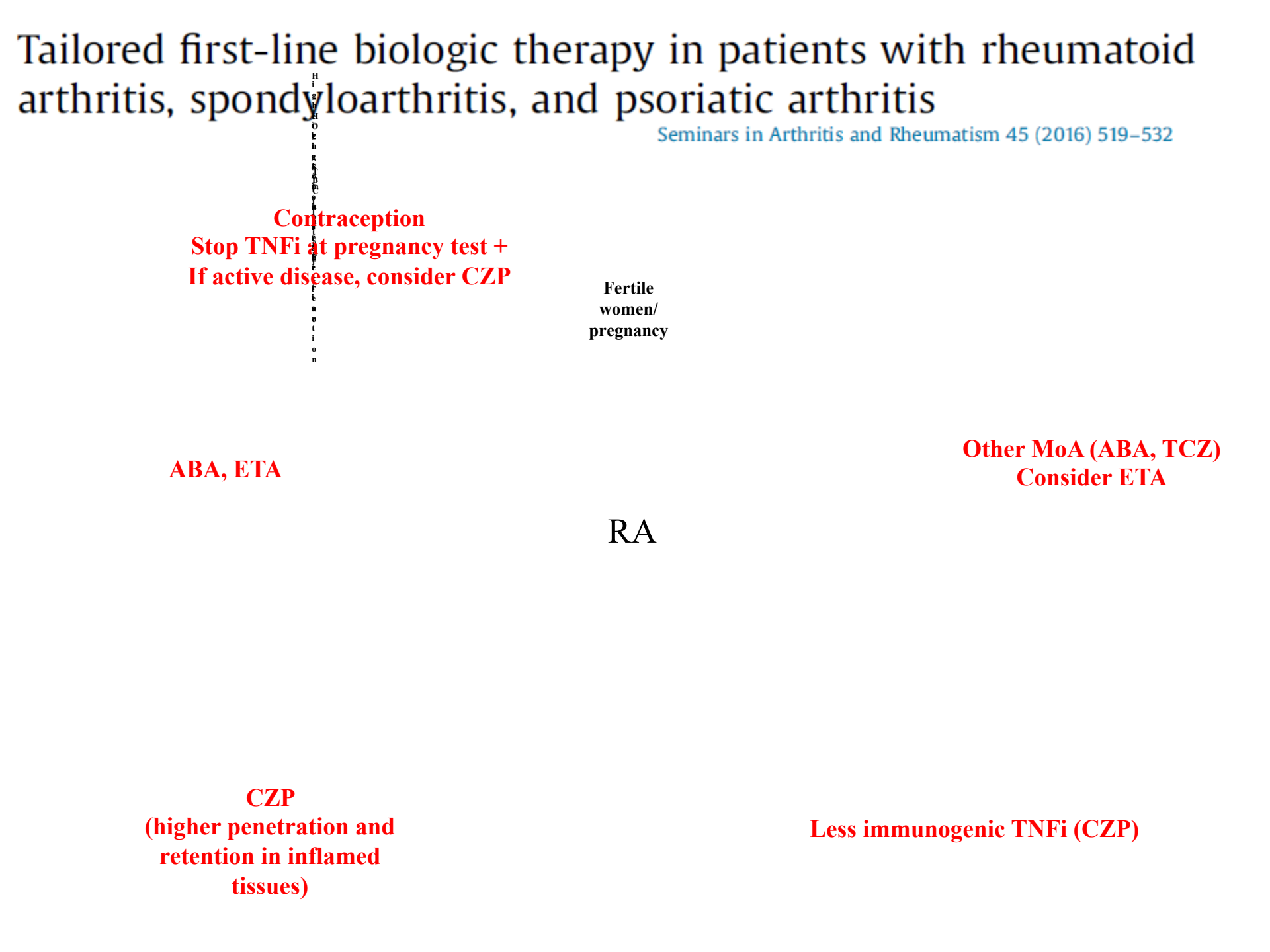
After



As shown in animal models, CZP penetrates inflamed joints more effectively than other TNFi.

Tailored first-line biologic therapy in patients with rheumatoid arthritis, spondyloarthritis, and psoriatic arthritis

Seminars in Arthritis and Rheumatism 45 (2016) 519–532



Tailored first-line biologic therapy in patients with rheumatoid arthritis, spondyloarthritis, and psoriatic arthritis

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- **Consider patients' characteristics, preferences and compliance**

Conclusions

- Differences among TNFis in structures and mechanisms of action may be responsible for differences in efficacy and tolerability issues.

- In some clinical setting, TNFi choice might be oriented.

- Due to its unique structure, CZP might be considered in case of (planned) pregnancy, single site inflammation, higher risk of allergic reaction.

- ETA could be considered in case of latent TBCi.