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The effect of DMARDs on immunogenicity of anti-TNFs

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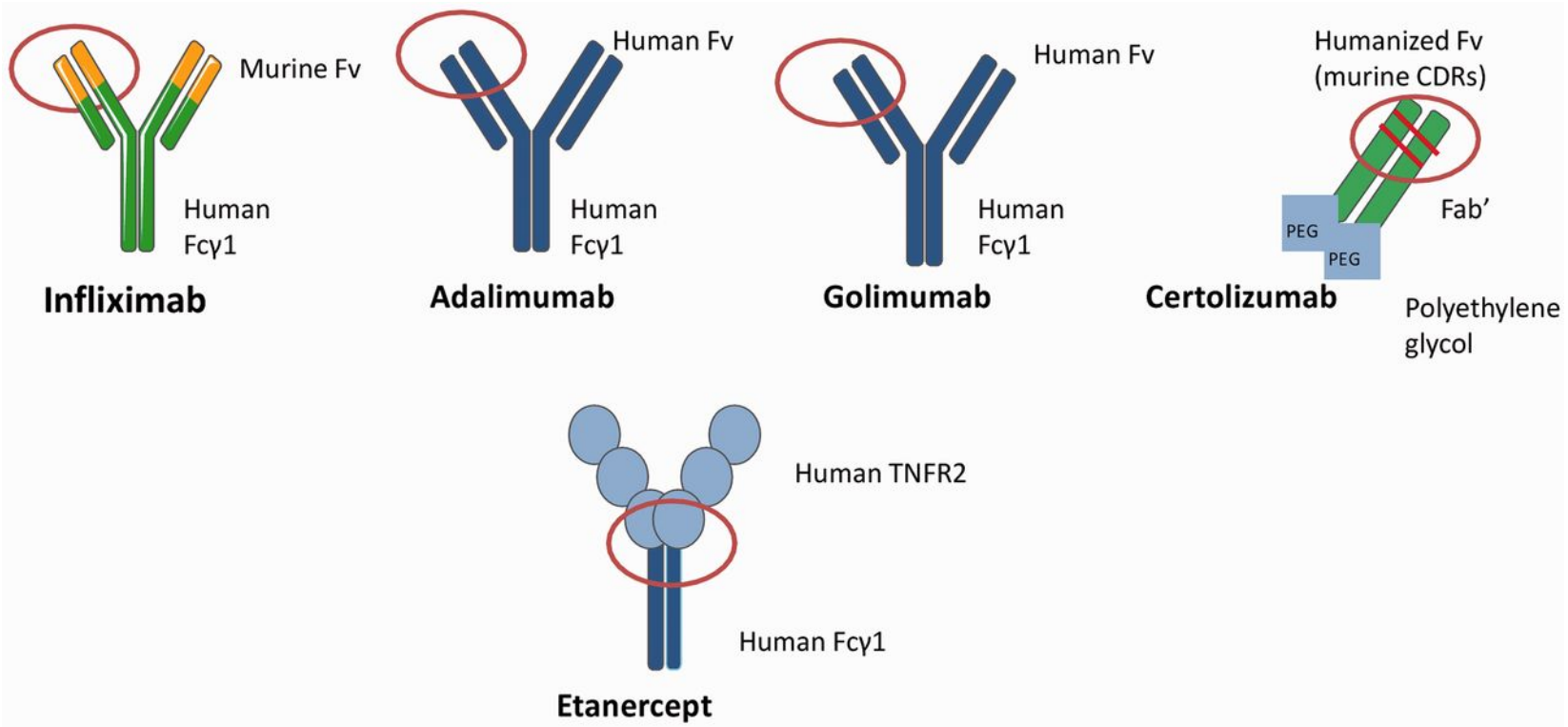
Biologics in clinical practice

- Biologics have transformed the treatment of RA, PsA, AS over the last decade
- Costs ≈ £10,000 per patient/year; serious adverse events
- 30-40% will not respond to anti-TNFs
- Some patients do not respond at all (primary non response)
- Some lose response (secondary non response)
- Mechanisms underlying these treatment failures are not entirely clear

Molecular structure of anti-TNF drugs with potential immunogenic sites



Jani M *et al.* Rheumatology 2014;53:213-222

Clinical consequences of immunogenicity

Efficacy

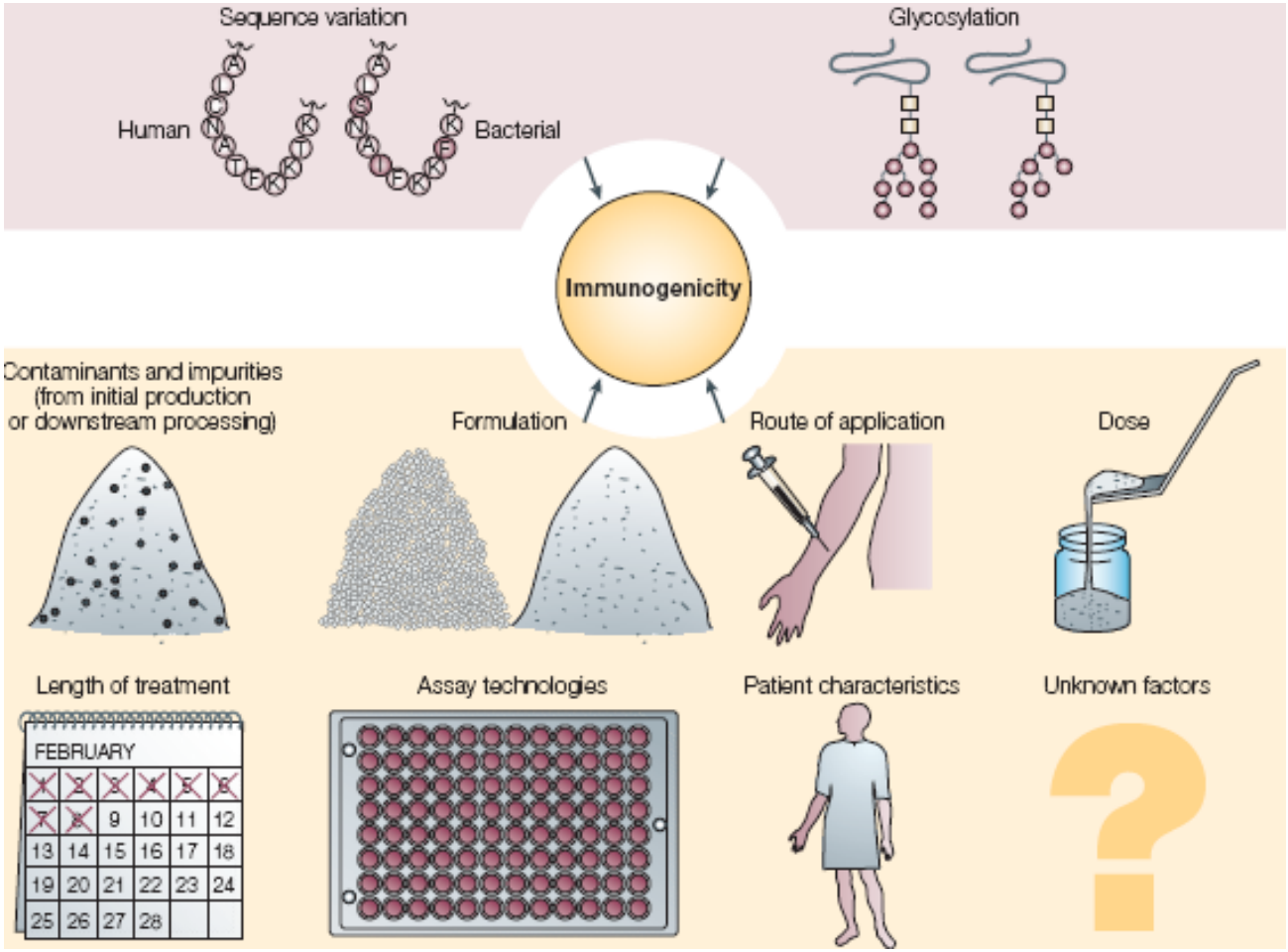
- Neutralizing antibody production leading to inefficacy

Safety

- Infusion site reactions
- Phenomena mediated by immune complexes (serum sickness, bronchospasm) in RA/ Crohn's
- Possible increase in arterial and venous thromboembolism[1]

[1] Korswagen LA *et al.* Arthritis Rheum 2011; 63:877-83

Factors influencing immunogenicity



Schellekens H. *Nat Rev Drug Discov* 2002:457–62

Treatment related factors

Detection of anti-drug antibodies	Drug-related factors	Individual characteristics	Treatment-related factors
Type of assay	Contaminants in the formulation process	Immunocompetence of the patient	Dose and frequency of drug
Timing of blood sample	Structural properties	Genetic predisposition	Route of administration
Duration of treatment	Sequence variation/murine components	Unknown factors	Use of concomitant immunomodulatory drugs
	Target binding ability		
	T cell epitopes		

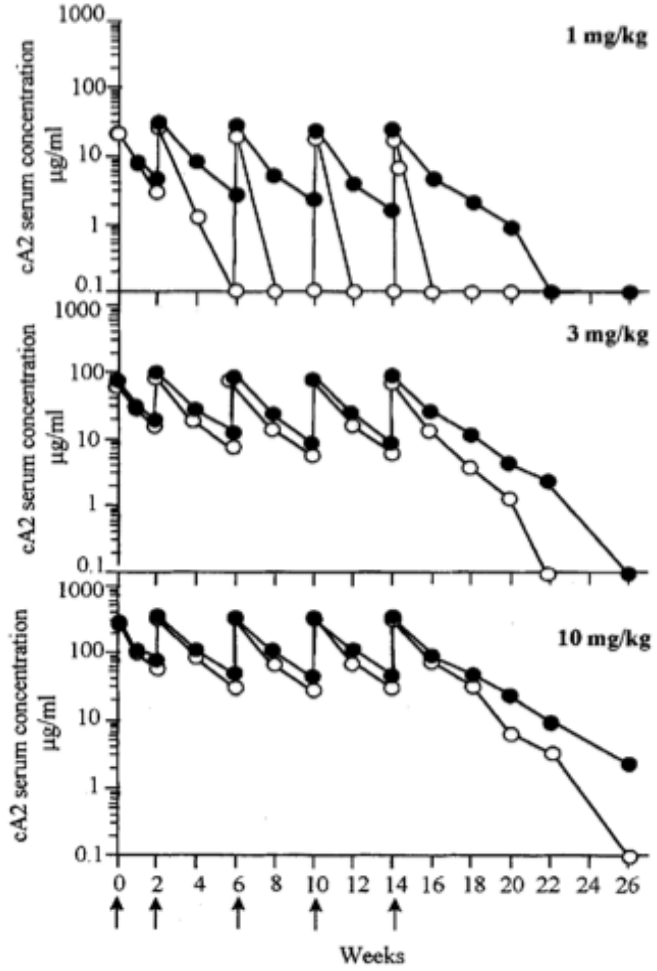
Jani M *et al*. Rheumatology 2014;53:213-222

Decision to start disease modifying anti-rheumatic drugs (DMARD)

- Often depends on adverse reactions, comorbidities, patient preference
- RA patients should be on MTX alongside anti-TNF drug
- In ankylosing spondylitis- not routinely prescribed
- In psoriasis- discontinued prior to starting biologic

Effect of MTX in IFX treated RA patients

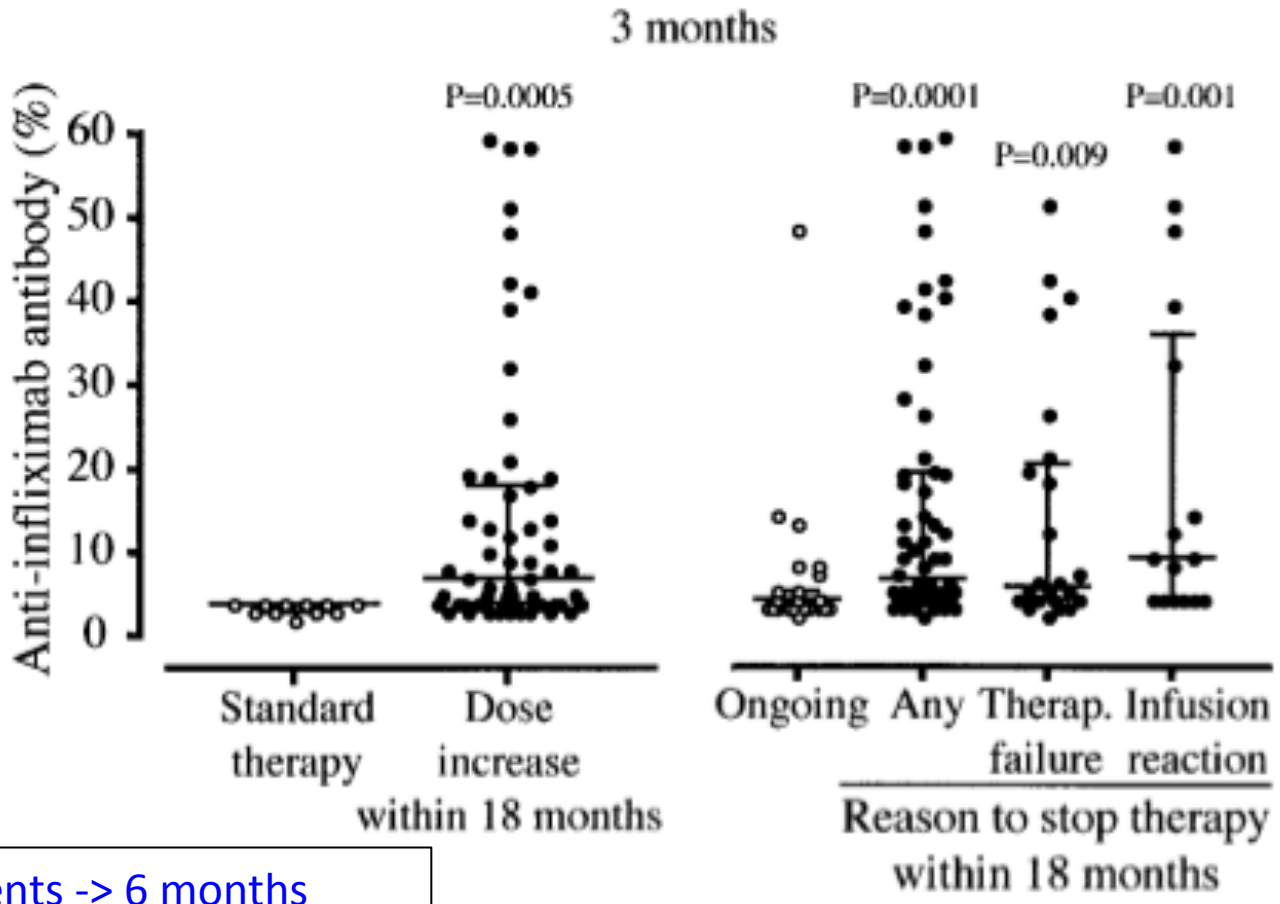
- MTX + INF
- No MTX



HACA 53% (no MTX)
vs. 15% (with MTX)

Maini R *et al*. Arthritis & rheumatism 1998; 41:1552-63

MTX lowering ADA levels



106 RA patients -> 6 months
MTX lowered ADAb levels, unlike any other DMARD

Bendtzen K *et al.* Arthritis Rheum 2006;54:3782-9

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"Development of Antidrug Antibodies against Adalimumab and association with Disease Activity & Treatment Failure during long-term follow-up"

272 consecutive RA patients:

148 (55%) completed follow-up, median FU 156 weeks

Fulfilled ACR 1987 revised criteria for RA & DAS28 ≥3.2 (active disease), despite treatment with 2 DMARDs

Treated with adalimumab (± DMARDs) 40mg subcut

TNF naïve or switchers → Adalimumab

Bartelds *et al*. JAMA. 2011;305(14):1460-8

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Methods

- Trough serum adalimumab concentrations measured by enzyme linked immunosorbent assay (ELISA)

- Radio immunoassay (Sanquin) used to detect presence of anti-adalimumab antibodies (ADA)

- All baseline samples before start of treatment were negative for ADA

- Patients were defined as positive for AAA if titres were > 12 AU/mL on at least 1 occasion *in combination with* serum adalimumab levels < 5.0 mg/L

Bartelds *et al*. JAMA. 2011;305(14):1460-8

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Results (1)

Table 1. Demographic and Clinical Characteristics at Baseline

Characteristics	Total Patient Population (N = 272)	Patients With Antiadalimumab Antibodies (n = 76)[a]	Patients Without Antiada Antibodies (n = 196
Age, mean (SD), y	54 (12)	53 (13)	54 (11)
Women, No. (%)	219 (81)	62 (82)	157 (80)
DMARD therapy[b]			
Prior DMARDs, mean (SD)	3.1 (1.4)	3.4 (1.5)[c]	3.0 (1.3)[c]
Prior biologics, No. (%)	75 (28)	25 (33)	50 (26)
Methotrexate use, No. (%)	202 (74)	41 (54)[c]	161 (82)[c]
Methotrexate dose, median (IQR), mg/wk	25 (15-25)	18 (10-25)[c]	25 (15-25)[c]
DMARD use other than methotrexate, No. (%)	19 (7)	7 (9)	12 (6)
Methotrexate plus other DMARD use, No. (%)	55 (20)	8 (11)[c]	47 (24)[c]
No concomitant DMARD, No. (%)	51 (19)	28 (37)[c]	23 (12)[c]
Prednisone use, No. (%)	91 (34)	27 (36)	64 (33)
Prednisone dose, median (IQR), mg/d	7.5 (5-10)	7.5 (5-10)	5 (5-10)
Disease status			
Disease duration, median (IQR), y	8 (3-17)	12 (5-18)[c]	8 (3-16)[c]
Rheumatoid factor positive, No. (%)	196 (72)	57 (75)	139 (71)
Anti-CCP positive, No. (%)	196 (72)	55 (72)	141 (72)
Erosive disease, No. (%)	201 (74)	63 (83)[c]	138 (70)[c]
ESR, median (IQR), mm/h	23 (11-42)	35 (18-60)[c]	21 (11-39)[c]
C-reactive protein, median (IQR), mg/L	12 (5-29)	19 (7-46)[c]	11 (4-22)[c]

Bartelds *et al*. JAMA. 2011;305(14):1460-8

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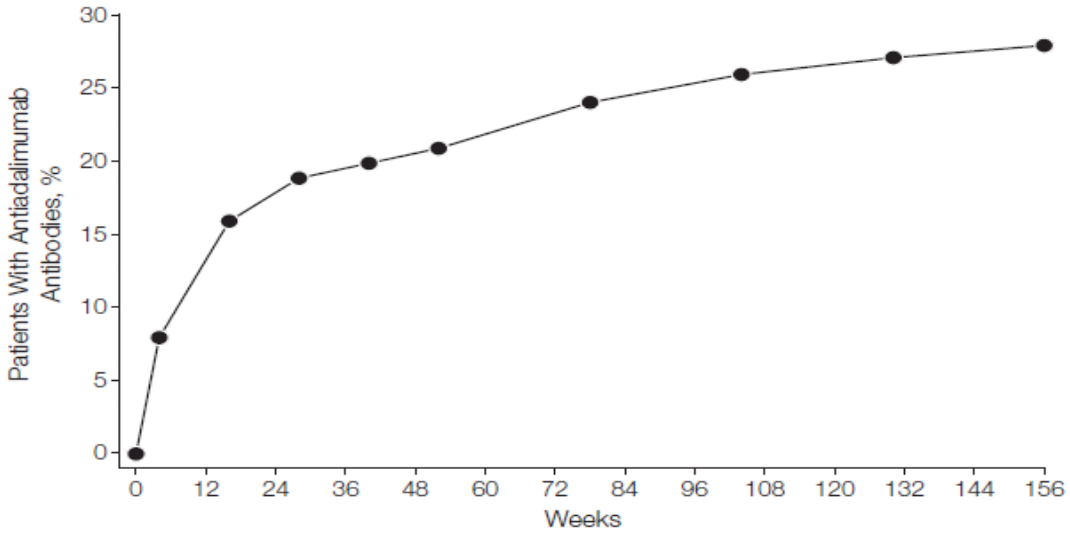
Results (2)

Figure 1. Percentage of Antiadalimumab Development Over Time



Week	0	4	16	28	40	52	78	104	130	156
No. of patients	272	261	247	228	201	192	175	156	137	118

Number of patients with available serum samples are shown.

Anti-adalimumab antibodies were detected in 76 patients (28%).

67% of ADA positive patients developed ADA during the first 28 weeks of treatment

Presence of ADAb was strongly associated with discontinued Rx due to drug inefficacy

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MTX dose response relationship on ADAb level

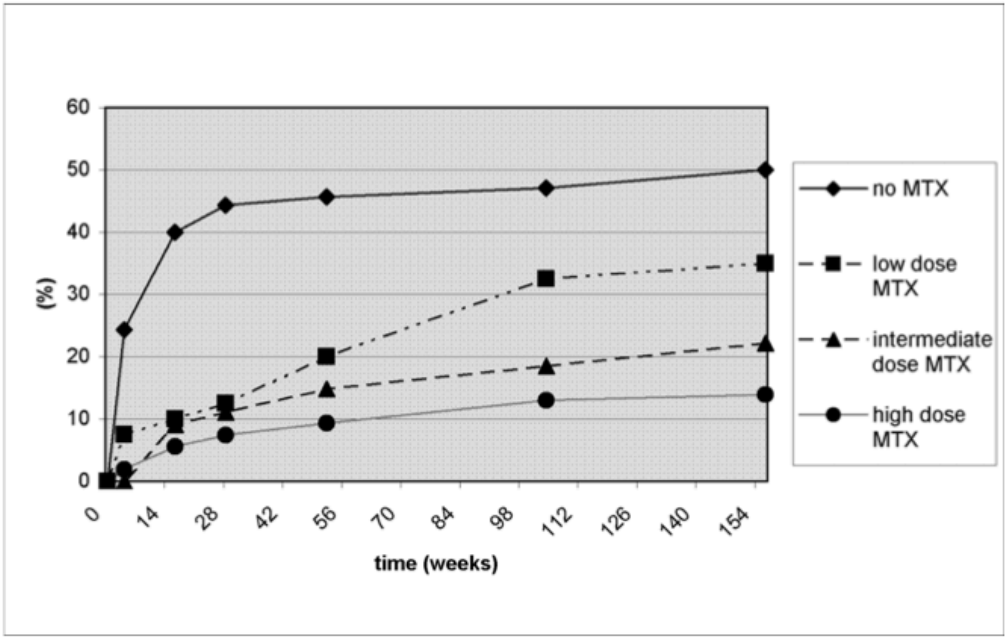

Figure 1 Percentage of patients developing antiadalimumab antibodies (AAA) per baseline methotrexate (MTX) dose group. No MTX (0 mg/week, n=70), low dose MTX (5–10 mg/week, n=40), intermediate dose MTX (12.5–20 mg/week, n=54), or high dose MTX (≥22.5 mg/week, n=108).

Krieckaert CL *et al.* Ann Rheum Dis 2012; 71: 1914-5

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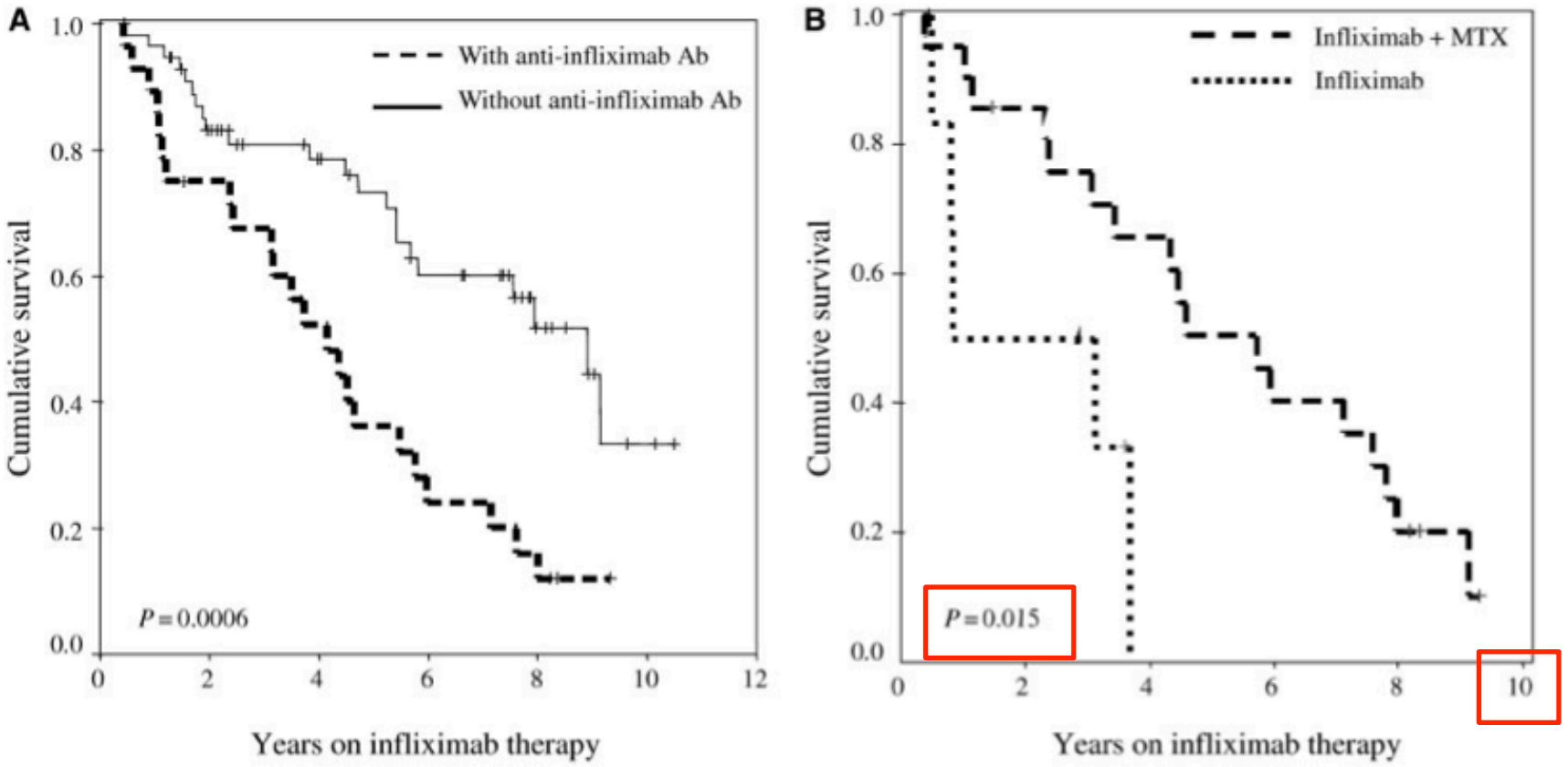
MTX effect on drug survival



Pascual-Salcedo D *et al.* Rheumatology 2011;50:1445-1452

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Real life clinical experience in UK

311 RA patients

Serum samples at 3, 6 & 12 months

Sanquin

- ADAb measured using RIA
- Drug levels using ELISA

(n=835 samples)

- Primary outcome DAS28 scores (disease activity of 28 joints)
- Multiple regression & generalized estimating equation used

Jani M *et al.* Unpublished Work 2014

Baseline Characteristics

Variables	Mean, SD (unless otherwise stated)
Age (years)	56 ± 13
Gender	75% female
Baseline DAS28 score (>5.1 indicates high disease activity)	5.9 ± 0.8
Disease duration (years, median IQR)	7 (3-15)
Concurrent DMARD (n, %)	281 (85)
Etanercept (n, %)	171 (51.7)
Adalimumab (n, %)	160 (58.3)
BMI (median IQR)	27.5 (23.6-32.3)

Jani M *et al.* Unpublished Work 2014

Results (1)

- ADAbs to adalimumab detected in 24.8%

(31/125 patients at ≥ 1 time points by 12 months of treatment)

- Presence of ADAbs significantly associated with lower adalimumab drug levels

(*p* <0.0001; r_s -0.51; If ADAb titres>100AU p=0.0041; r_s-0.66)

- At 3 months, ADAb formation & low drug levels were a significant predictor of poor ΔDAS28 at 6 and 12 months

(*p*< 0.0001, RC -0.0048 95% CI: -0.0071 to -0.0025)

Jani M *et al.* Unpublished Work 2014

Results (2)

- Patients who did not develop ADAbs were more likely to be co-treated with MTX (61.4% vs. 43.7% p= 0.01)

- None of the etanercept patients had detectable ADAbs

- Low etanercept drug levels still associated with poor treatment response

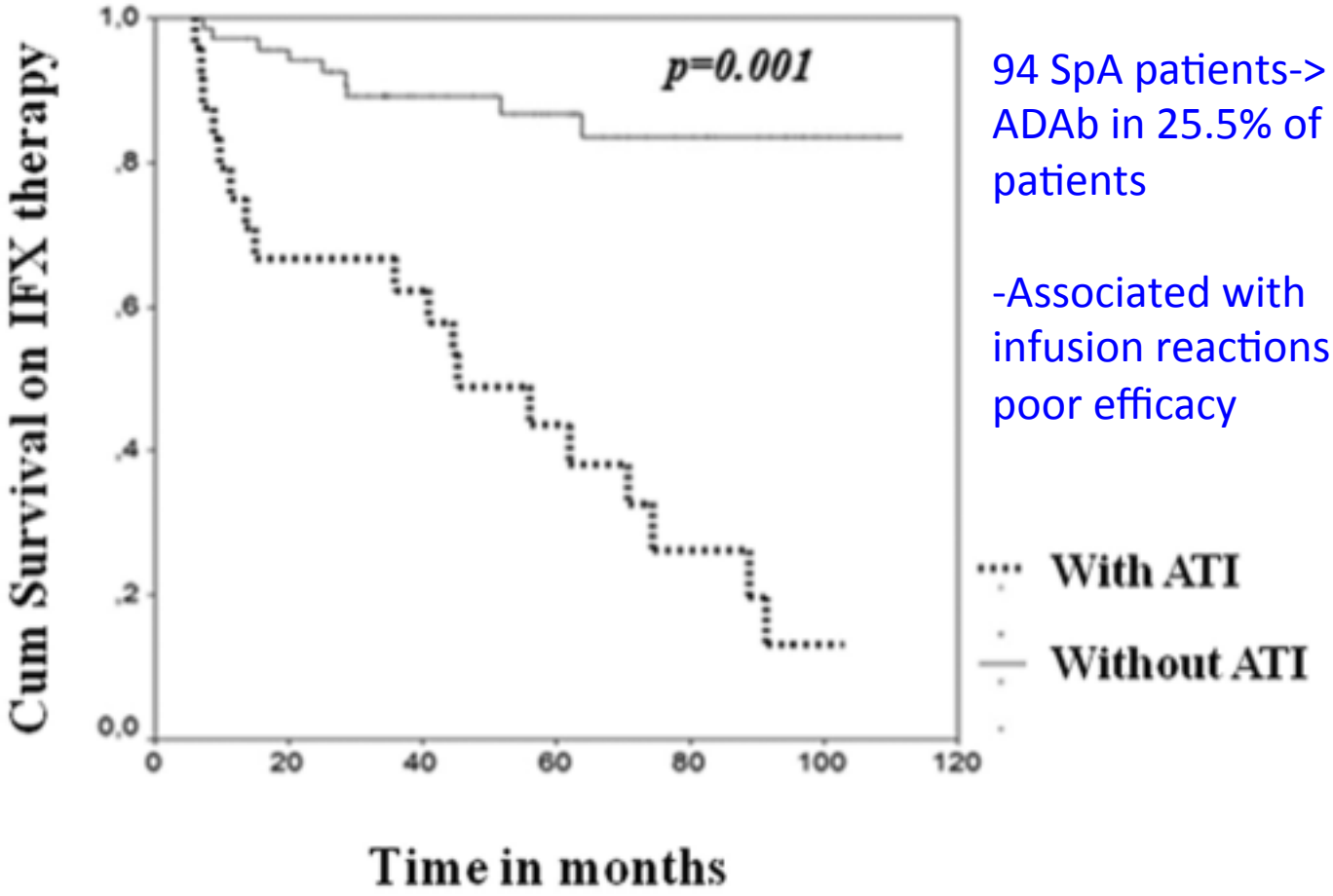
Jani M *et al.* Unpublished Work 2014

Newer MAbs

- Certolizumab pegol and golimumab- prospective observational studies lacking
- FAST4WARD trial- certolizumab monotherapy *vs.* placebo.
- 8.1% ADAb detected at 24 weeks
- Estimated 5% reduction in ACR20 [1]

[1] Fleischmann R *et al.* Ann Rheum Dis 2009; 68: 805-11

Ankylosing spondylitis & IFX



94 SpA patients-> ADAb in 25.5% of patients

-Associated with infusion reactions & poor efficacy

ADAb in patients not taking MTX (34.5%) *vs.* taking MTX (11.1%) (p=0.011)
MTX delayed the appearance of ADAb formation

Plasencia C *et al.* Ann Rheum Dis 2012 Dec;71(12):1955-60

Psoriasis

- The addition of MTX (5-15mg/kg) even after development of ADAb to IFX reduced PASI score and disappearance of ADAb in 8 weeks[1]

- 80 patients on adalimumab- > 12 months[2]
- ADAbs developed in 49% of patients (90% in 6 months)
- MTX Rx in 8 patients (none developed high titre ADAbs)
- MTX initiated after ADAb formation in 2 patients (n=1 -> responder; high-> low ADAb titres)

1 Adisen E *et al.* Journal of Dermatology 2010; 37: 708–713
2 Menting S *et al.* JAMA Dermatol. 2014;150(2):130-136

MOA methotrexate

- Concomitant DMARD including MTX can reduce ADAb by 41% (37-> 64% assay dependent)[1]
- Anti-inflammatory and immunomodulatory
- May affect T & B cell expansion
- Synergistic effect- reducing TNF burden
- Polyglutamation of MTX associated with improved PK profile of IFX and lower immunogenicity [2]

[1] Garcês S *et al.* Ann Rheum Dis. 2013 Dec;72(12):1947-55
[2] Dervieux T *et al.* Ann Rheum Dis 2013; 72:908-10

Other DMARDs

- Azathioprine reduces immunogenicity in Crohn's disease (similar to MTX)[1]
- Not sufficient evidence for use of azathioprine in RA
- Minimal evidence to suggest other DMARDs such as SZ, LEF, HCQ & steroids reduce ADAb and prolong drug survival

[1] Vermeire S *et al.* Gut 2007;56:1266-31

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Implications for future studies

- IFX biosimilar (CPT-13) tested in RA patients
- Immunogenicity profile should be studied "in the patient population that carries the highest risk of an immune response and immune-related adverse events" [1]
- Rheumatoid arthritis patients requirement to be on concomitant MTX
- Extrapolation to other indications may underestimate immunogenic potential of new drug

[1] WHO. Guidelines on evaluation of similar biotherapeutic products. Geneva: 2009

Summary

- MTX reduces immunogenicity of monoclonal anti-TNF drugs in RA (SpA, psoriasis)
- Dose optimisation may prolong drug survival in RA patients
- Insufficient evidence at present to advocate all SpA and psoriasis patients receive MTX
- Future implications for biosimilar studies

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