Overzicht van het biologische landschap bij immuun-gemedieerde ziekten

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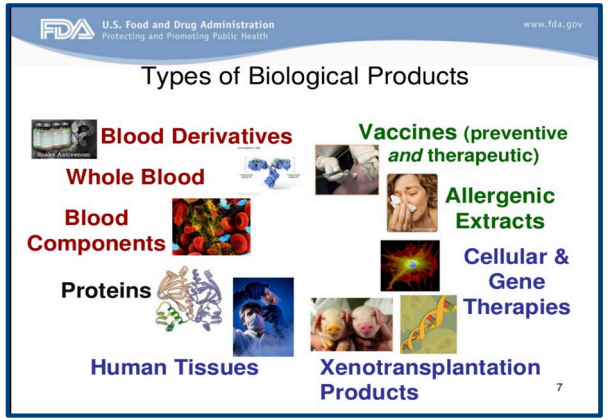
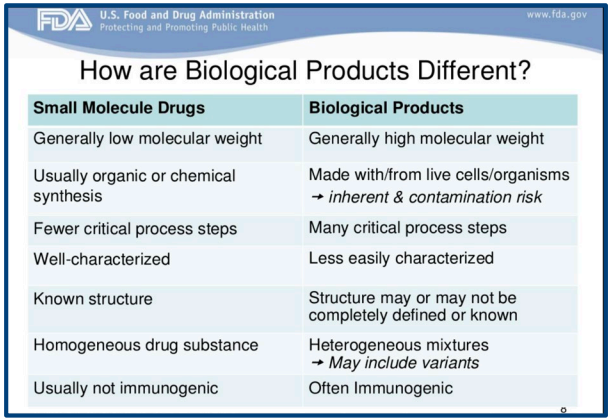
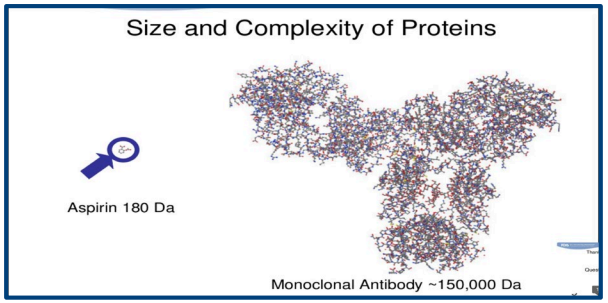
Pentalfa , Leuven 23 januari 2020

Biological: a substance of biological origine used as a drug , vaccine, pesticide,….





Small Molecule Drugs	Biological Products
Generally low molecular weight	Generally high molecular weight
Usually organic or chemical synthesis	Made with/from live cells/organisms → *inherent & contamination risk*
Fewer critical process steps	Many critical process steps
Well-characterized	Less easily characterized
Known structure	Structure may or may not be completely defined or known
Homogeneous drug substance	Heterogeneous mixtures → *May include variants*
Usually not immunogenic	Often Immunogenic



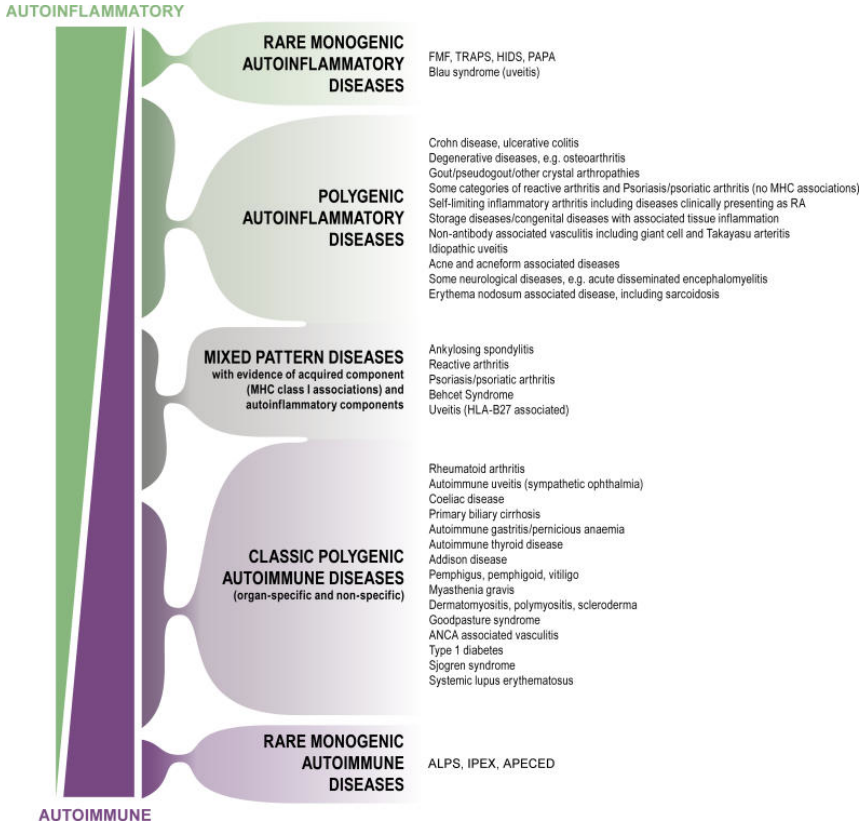
1986: IgG2 CD3 renal transplant
1997: Rituximab lymphoma
1998: Trastuzumab breast cancer

1998: Infliximab: Crohn's disease

Immuungemediëerde inflammatoire aandoeningen

- Aandoening waarbij ontstekingen ontstaan als gevolg van een ontregeld immuunsysteem.
- Verschillen
  - verschillende organen en ‘systemen’
  - binnen elke IMID zijn er verschillen
- Verband
  - genetische aanleg, soms overlappend
  - ontstekingen door een ontregeling van de immuunafweer
  - IMID geeft meer kans op 2^{e} IMID
- IMID’s gekenmerkt worden door soortgelijke ontregeling van het immuunsysteem: TNF-α, IL-17,….
- Orgaan behandeling evolueert naar proces (mechanistische) behandeling

Het spectrum van immuun gemedieerde ziekten



Rheumatoid arthritis

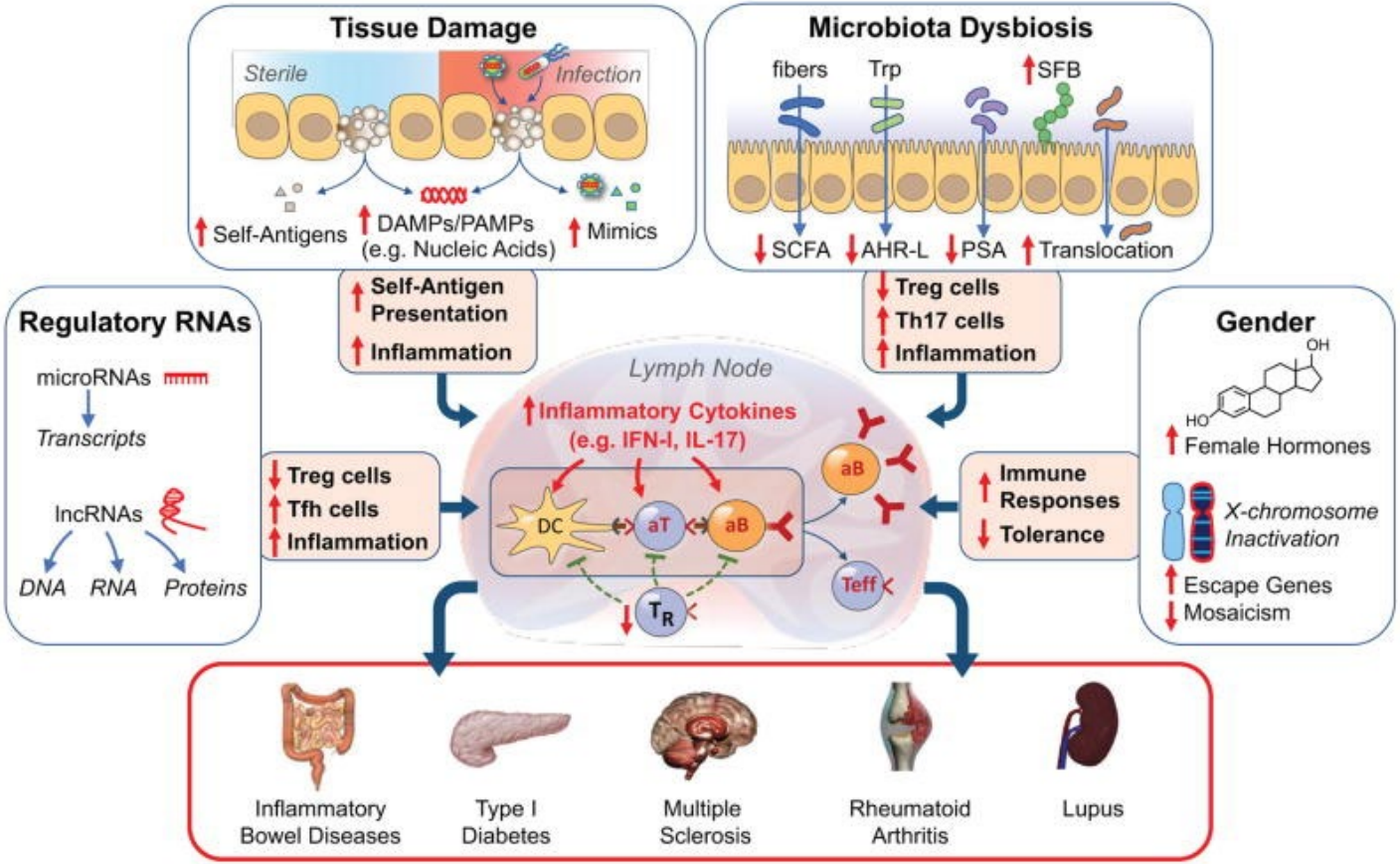
- Autoantibody identified
- MHC Class II (shared epitope) (self-non self)
- SS, vasculitis, nodules
- Type II collagen
- Homogeneous tissue response

Psoriatic arthritis

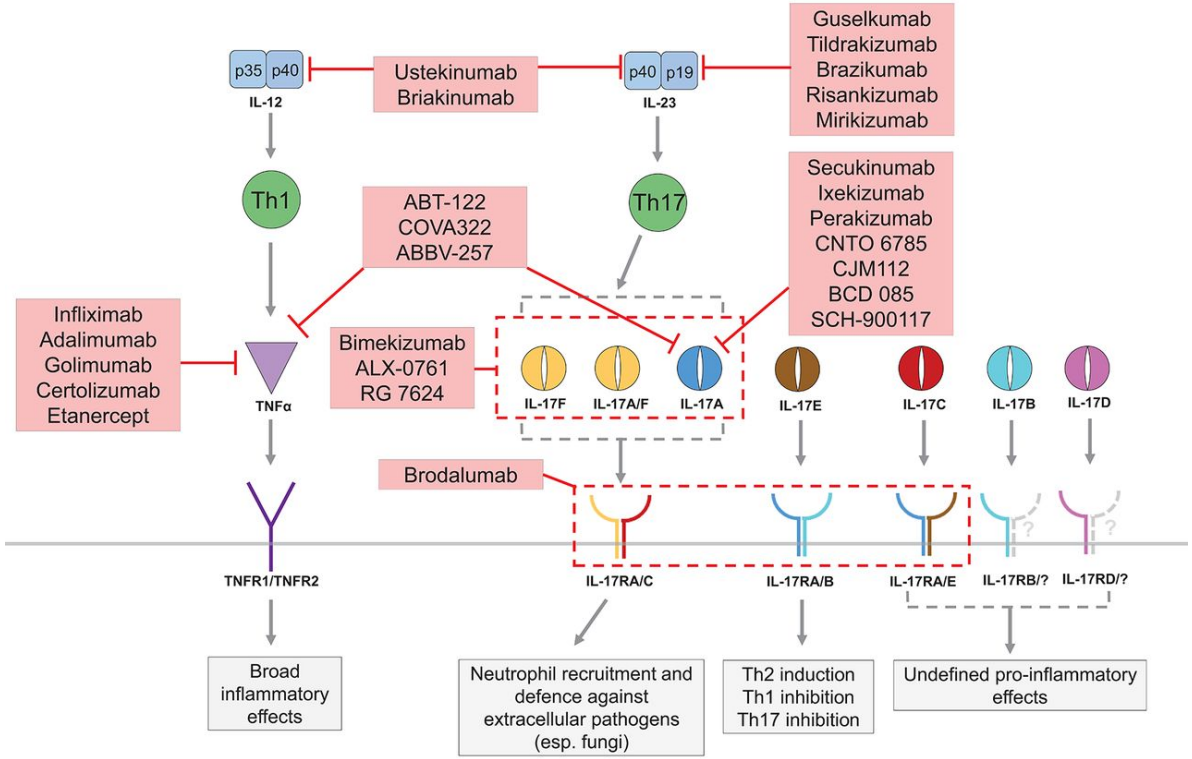
- No autoantibodies
- MHC class I
- Psoriasis, uveitis, IBD
- Over expression/deletion of GF, cytokines, signals
- Heterogeneous tissue response

McGonagle Plos Med 2006

Multipele pathways naar immuun gemedieerde inflammatie

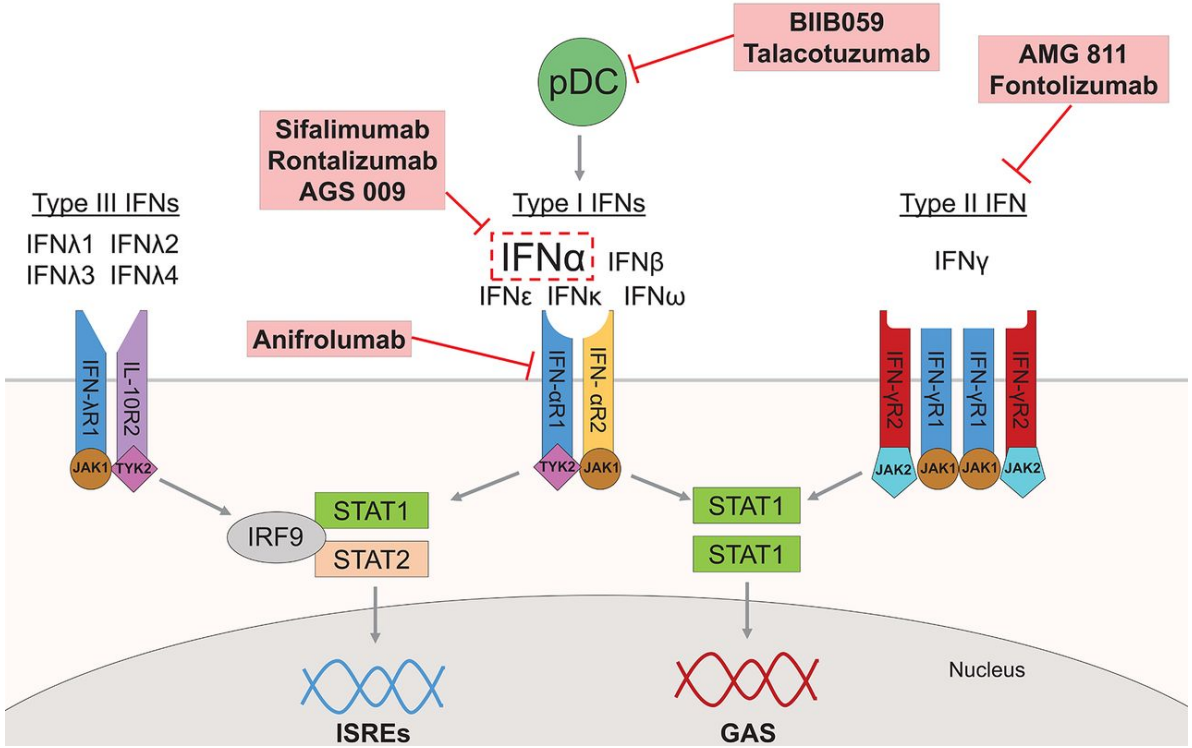


Overview of biologics targeted against elements of the T-helper (Th)17/interleukin (IL)-17 and tumour necrosis factor-α (TNF-α) axes.



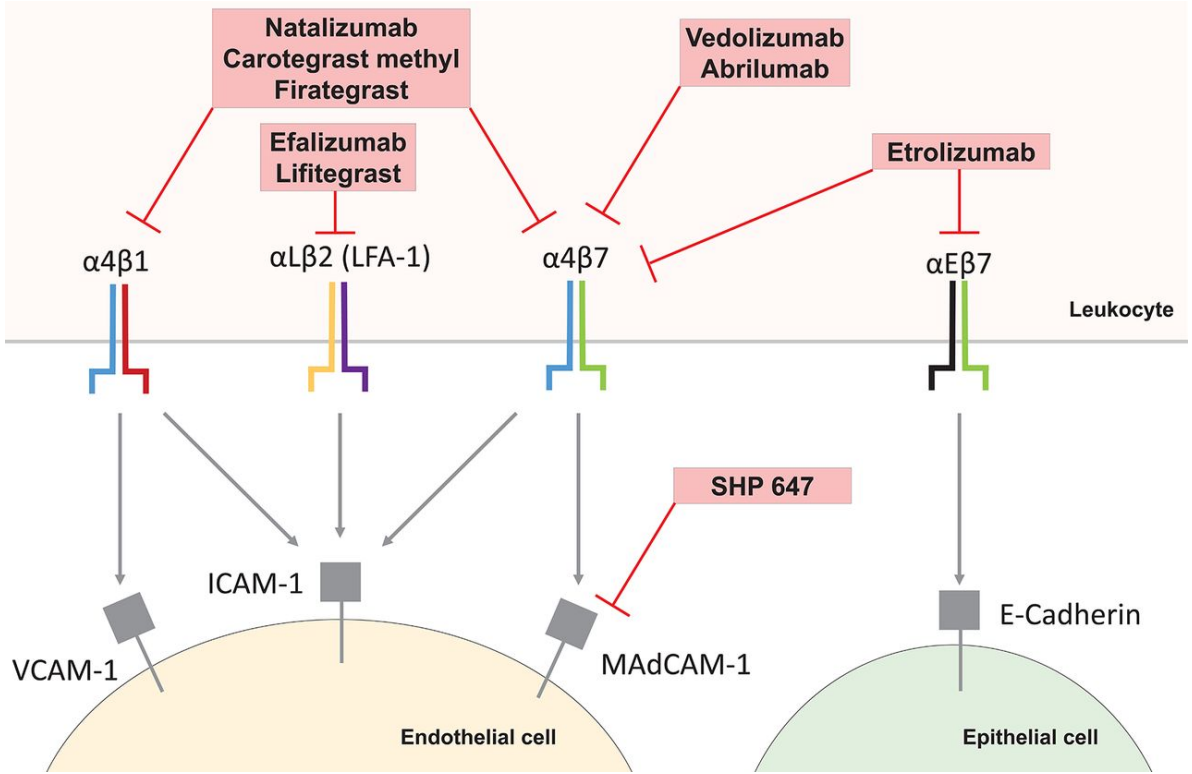
Kenneth F Baker, and John D Isaacs Ann Rheum Dis 2018;77:175-187

Overview of biologics targeted against interferon (IFN) pathways.



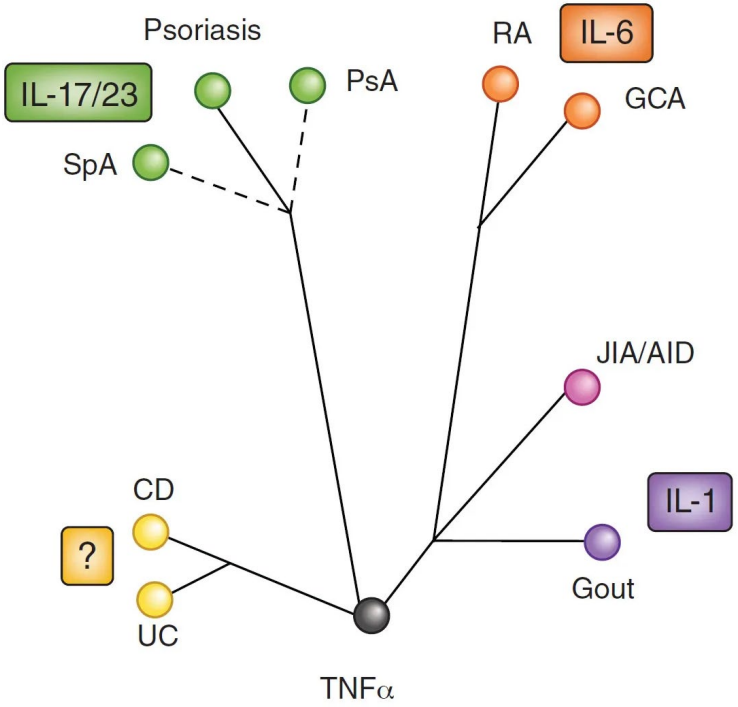
Kenneth F Baker, and John D Isaacs Ann Rheum Dis 2018;77:175-187

Overview of drugs targeted against integrin molecules and their ligands.



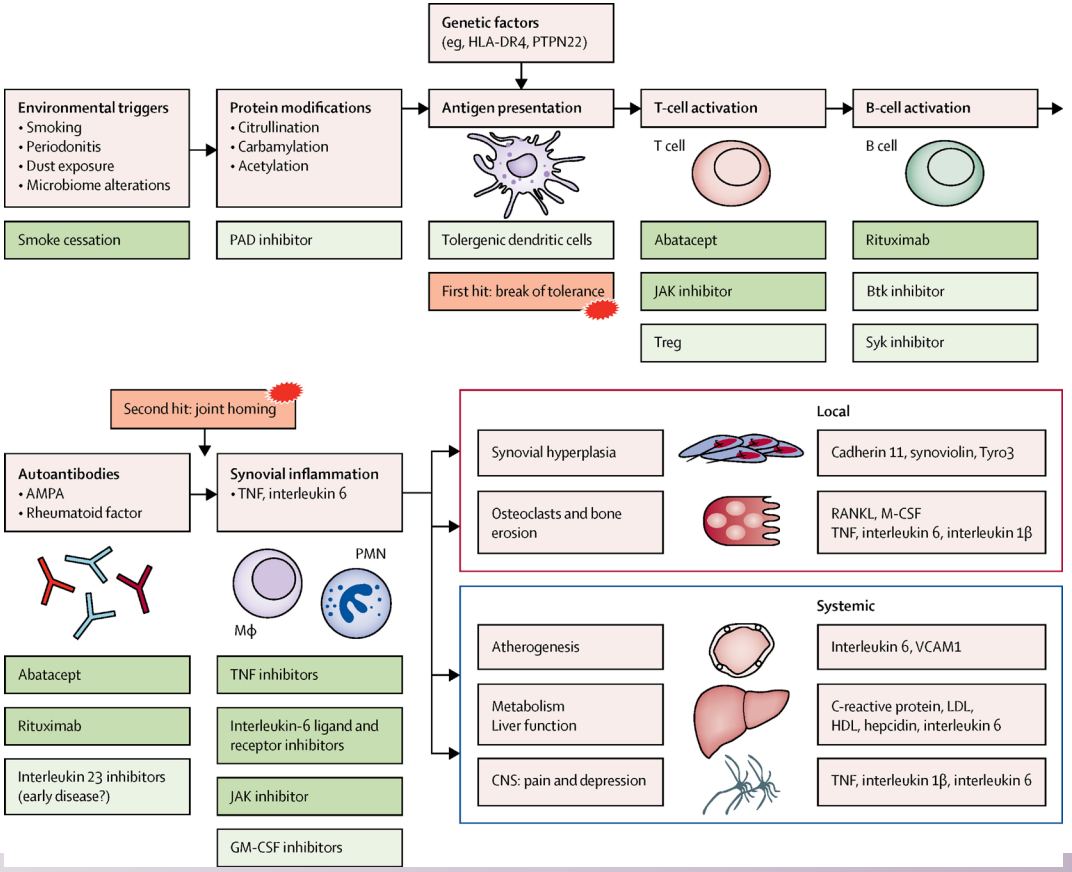
Kenneth F Baker, and John D Isaacs Ann Rheum Dis 2018;77:175-187

Common pathways amongst different diseases



Schett G,Nat Med. 2013

1 disease: different pathways



Anti-TNF
- Etanercept
- Infliximab
- Adalimumab
- Golimumab
- Certolizumab

Anti-IL6-receptor
- Sarilumab
- Tocilizumab

Anti-B cell
- Rituximab

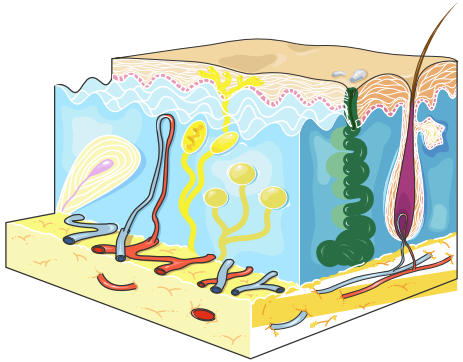
Anti-T cell costimulation
- Abatacept

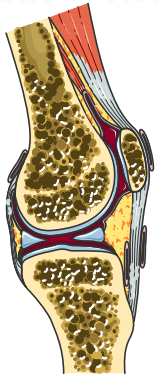
JAK inhibitors
- Tofacitinib
- Baricitinib
- Filgotinib

McInnes & Schett, Lancet 2017

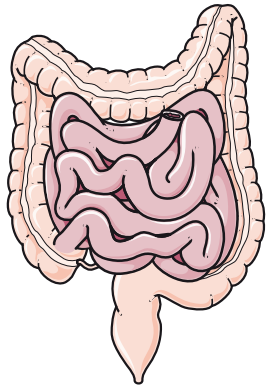
CID	TNF-α	IL-6R	IL-1	IL-12/23	IL-17A	IL-23	CD-20	α4-β7	CD86	BLys	RANKL
Rheumatoid arthritis											
Ankylosing Spondylitis /Spondyloarthropathy											
Psoriatic Arthritis											
JIA/AID											
Gout											
Giant Cell arteritis											
Crohn's Disease											
Ulcerative colitis											
Psoriasis											
Hydradenitis suppurativa											
Multiple Sclerosis											
uveitis											
SLE											
osteoporosis											
	Remicade Etanercept Adalimumab Certolizumab Golimumab Biosimilars	Tocilizumab Sarilumab biosimilars	Anakinra Canakinumab Rilonacept	Ustekinumab	Secukinumab Brodalumab Ixekizumab	Guselkumab Tildrakizumab Risankizumab	Rituximab biosimalars	Vedolizumab	Abatacept	Belimumab	Denosumab

Psoriasis	Psoriatic Arthritis	Axial SpA	Crohn's disease
anti-TNF	anti-TNF	anti-TNF	anti-TNF
anti-IL12/23	anti-IL12/23		anti-IL12/23
anti-IL-23	anti-IL-23	anti-IL-17	JAKi
anti-IL-17	Anti-IL-17		
PDE4i / JAKi	PDE4i / JAKi		







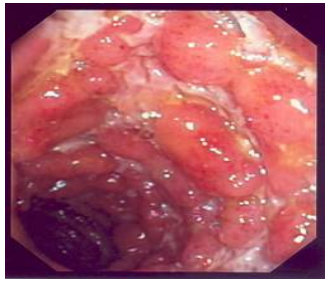


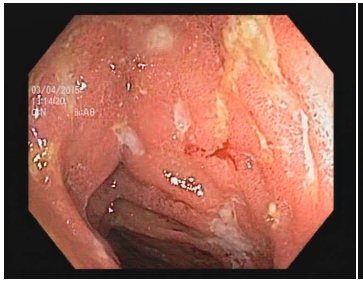
Anti TNF: infliximab, etanercept, adalimumab, certolizumab, golimumab
Anti IL12/23: ustekinumab ; Anti IL23: guselkumab
Anti IL17: secukinumab, ixekizumab PDE4i: apremilast JAKi: tofacitinib

Efficacy

Goal of installing a treatment = clinical remission off steroids + endoscopic healing

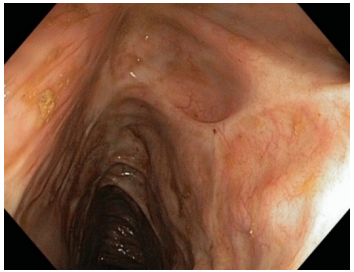


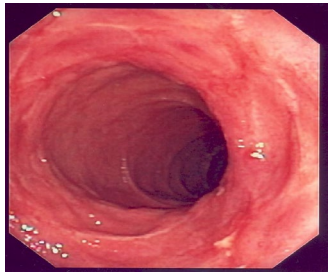


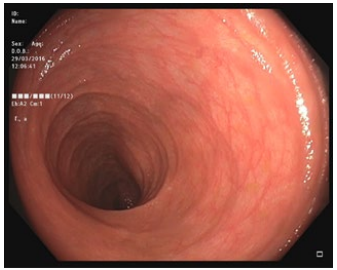




azathioprine **infliximab** **vedolizumab** **ustekinumab**

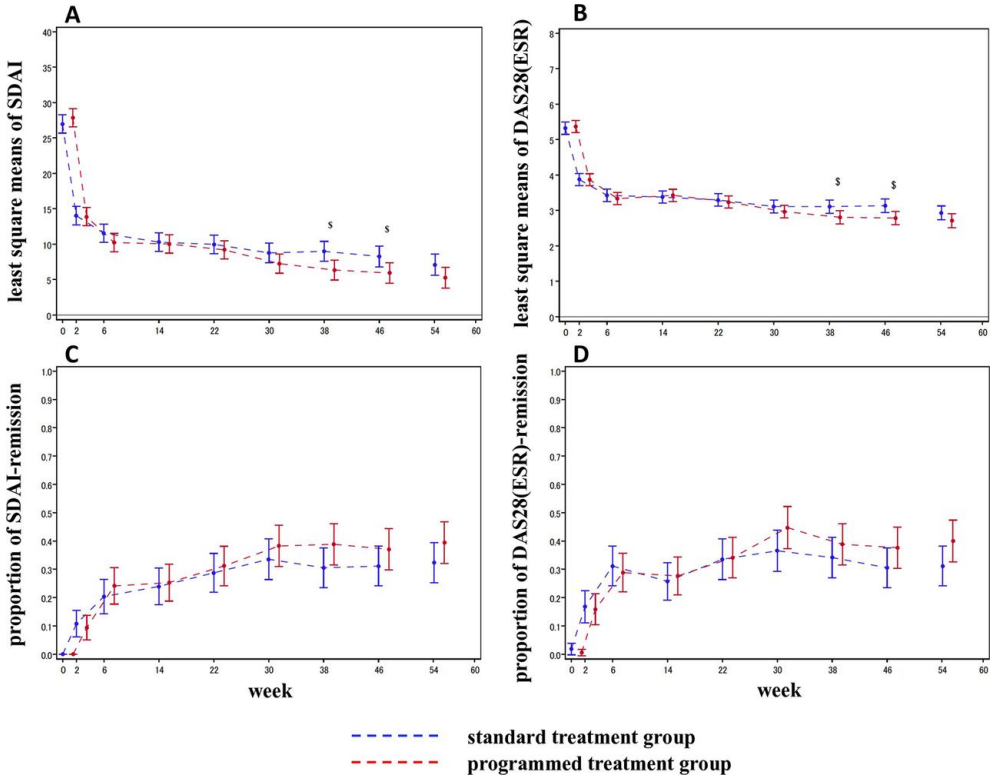






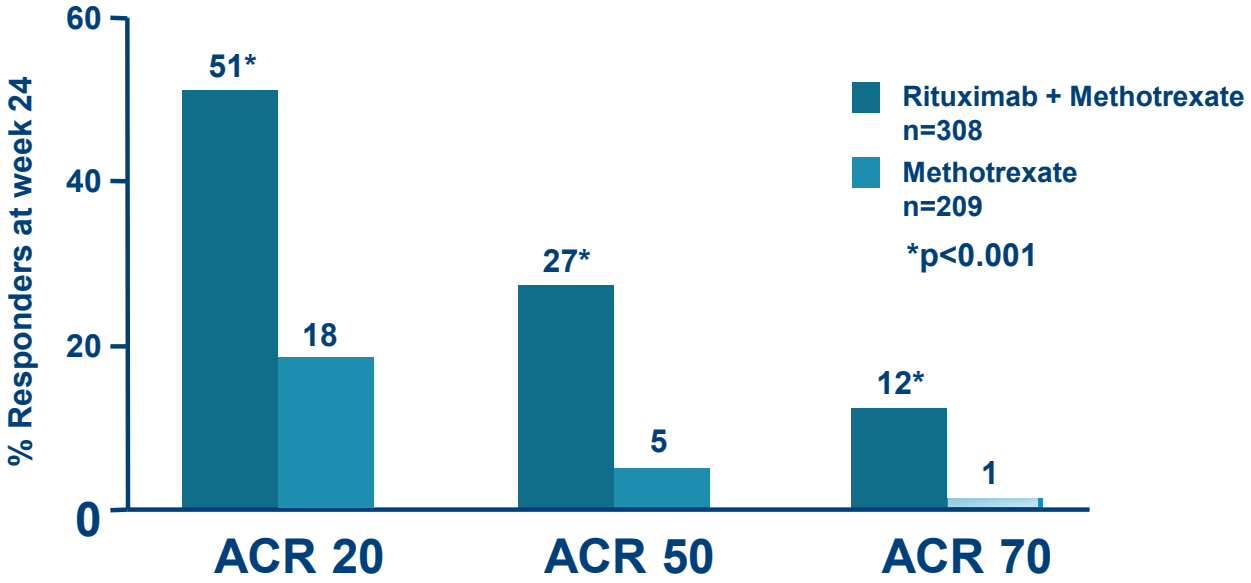


Change from baseline in SDAI (A) and DAS28-ESR, and proportion of remission based on SDAI (C) and DAS28-ESR (D).



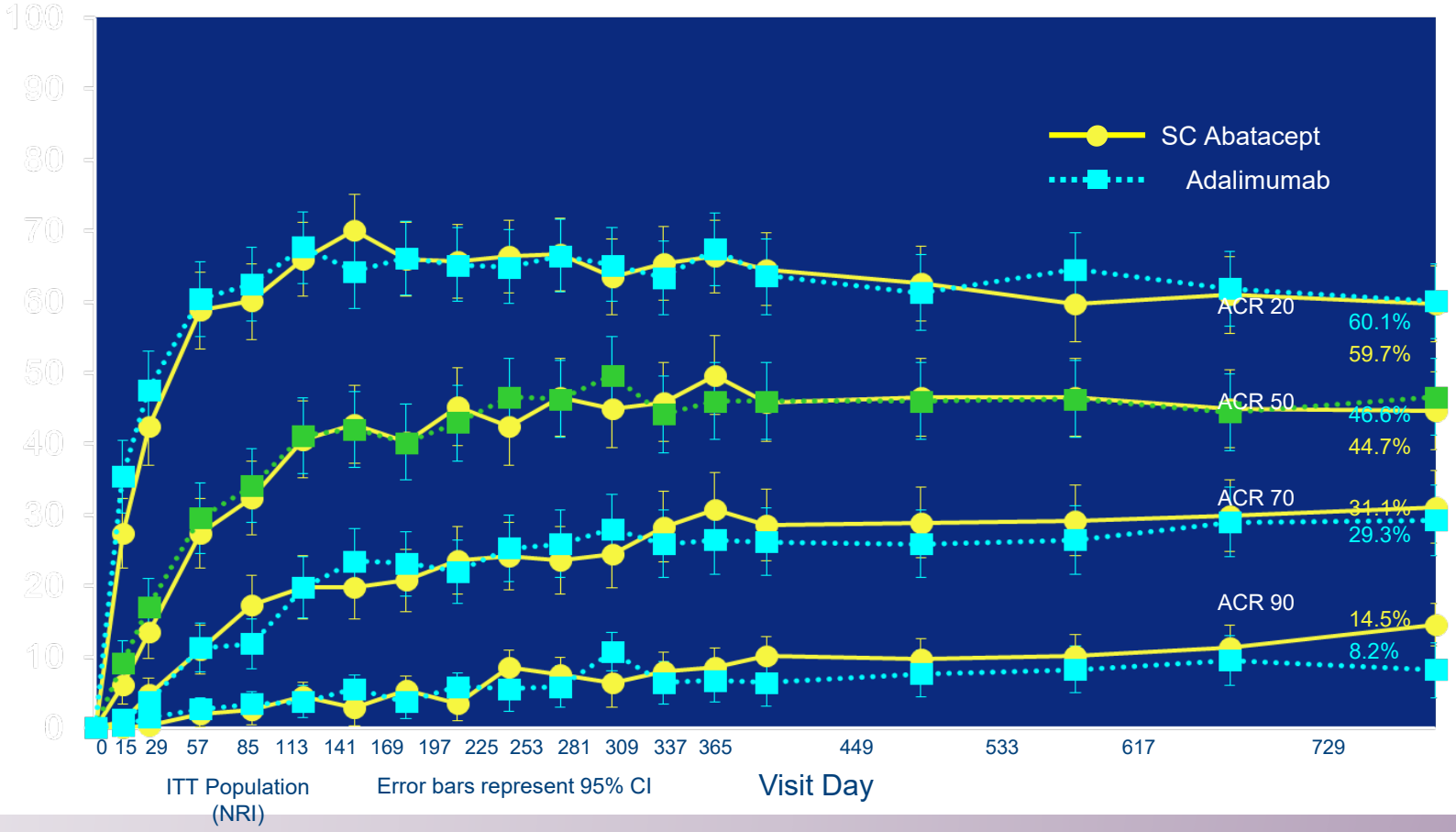
Yoshiya Tanaka et al. Ann Rheum Dis 2020;79:94-102

REFLEX trial – significant ACR response at Week 24: the Rituximab story



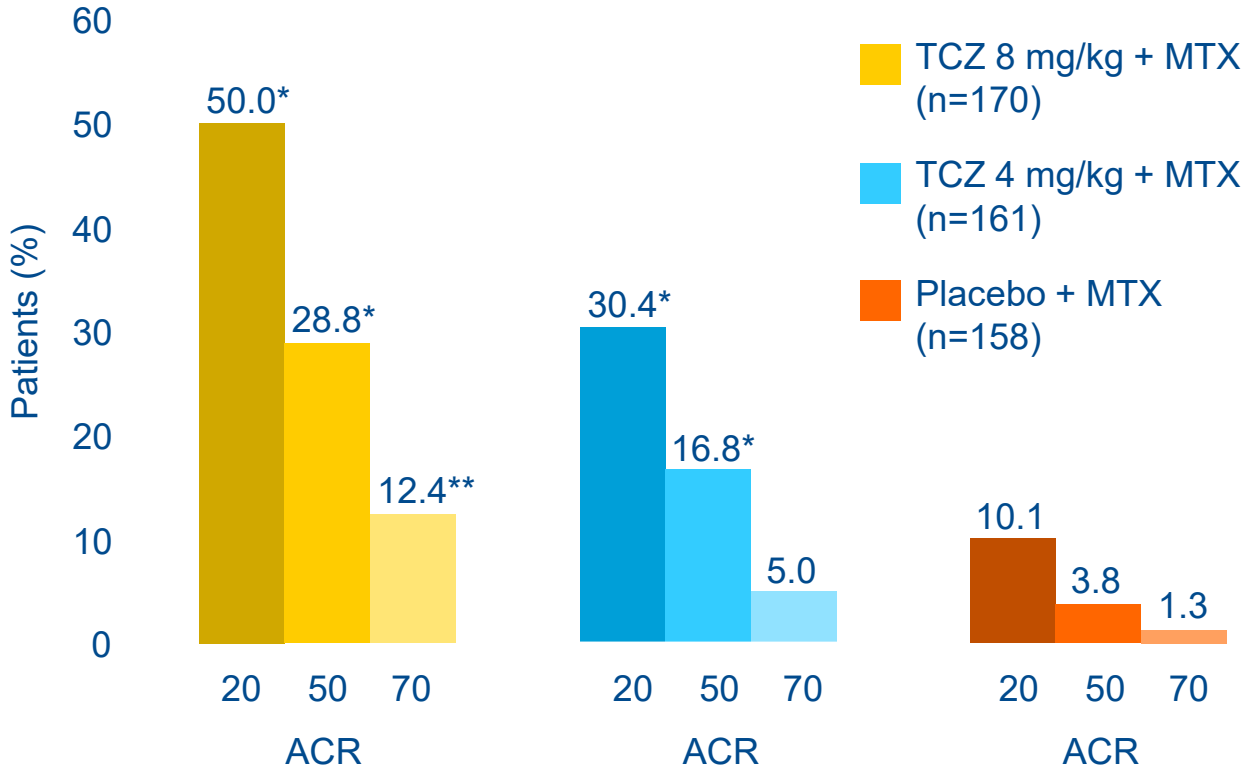
Cohen SB et al. Arthritis Rheum 2006;54:2793–806

Comparable Efficacy and Kinetics of Response: ACR Scores Over 2 Years



Schiff M. et al. Ann.Rheum.Dis Ann Rheum Dis. 2014 Jan;73(1):86-94

ACR response at Week 24 (ITT) RADIATE: the Tociluzimab story

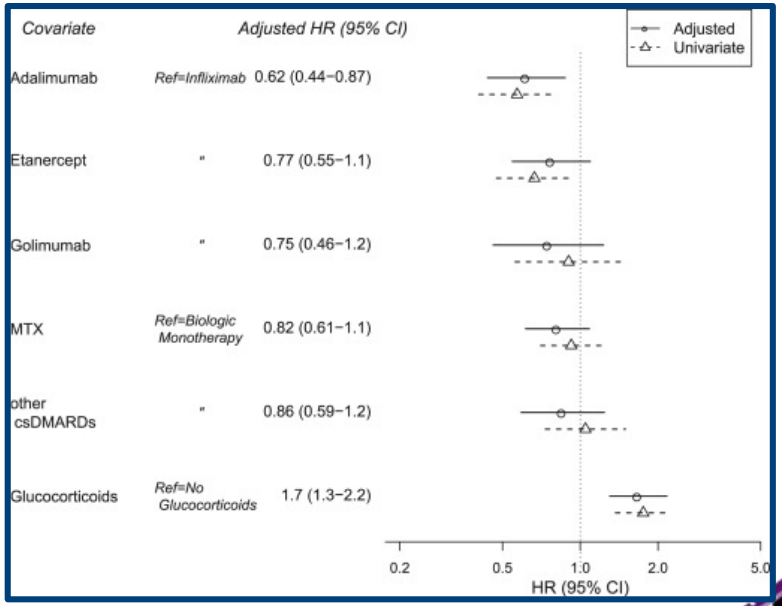


*p<0.0001 versus placebo + MTX; **p<0.01 versus placebo + MTX

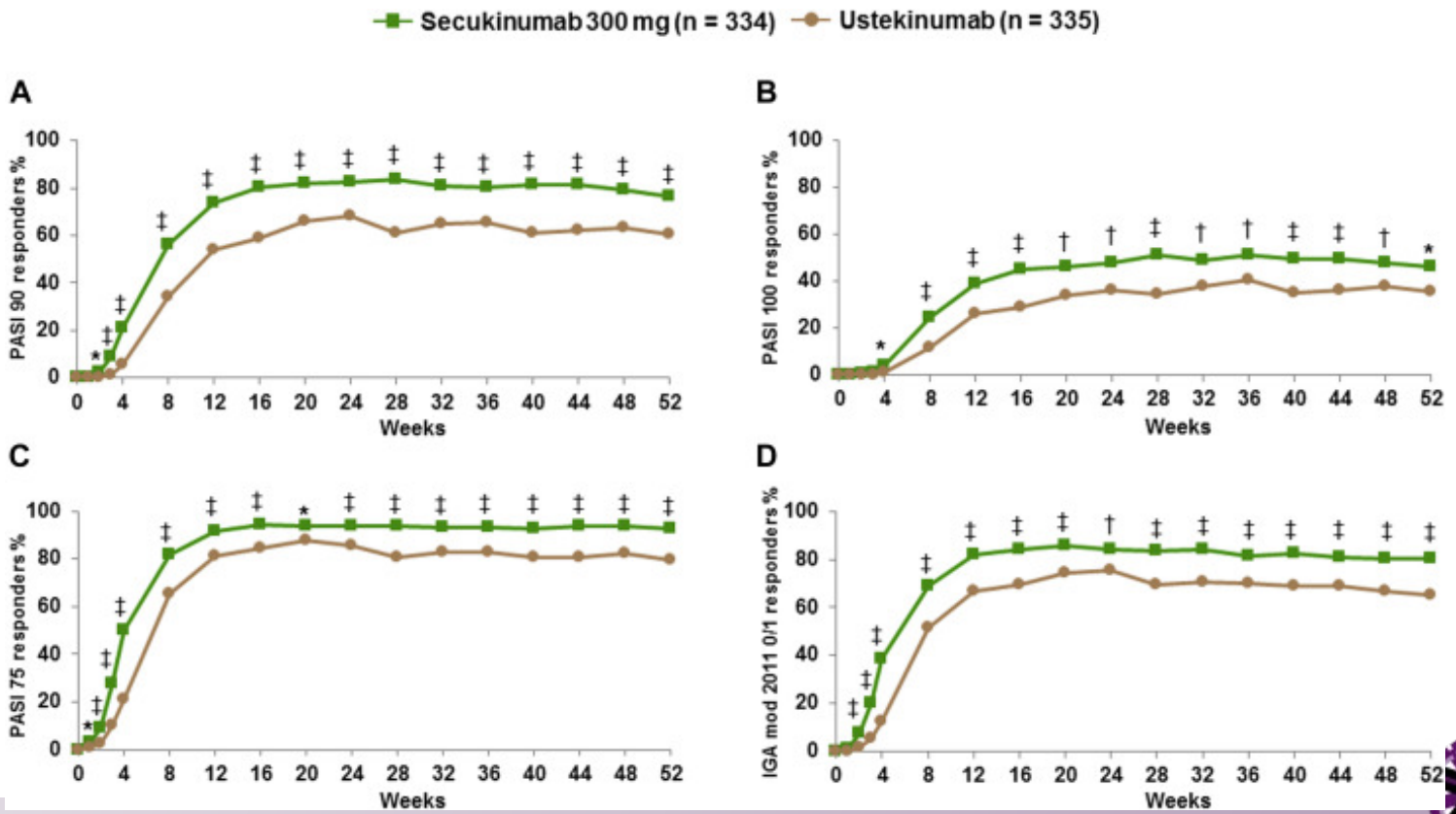
Emery P et al Ann Rheum Dis. 2008 Nov;67(11):1516-23

Drug survival: discontinuation of anti TNF in PsA

	3 Months	6 Months	12 Months	24 Months	36 Months
TNF-inhibitors used as the first bDMARD %, (95% CI)					
Adalimumab	1.9 (0.11–3.7)	7.8 (4.2–11)	16 (11–20)	24 (17–29)	29 (22–35)
Etanercept	5.2 (2.3–8.0)	9.5 (5.6–13)	15 (10–20)	24 (18–29)	30 (23–36)
Golimumab	9.4 (0–19)	13 (0.24–24)	26 (8.8–40)	26 (8.8–40)	26 (8.8–40)
Infliximab	5.2 (0.93–9.2)	9.2 (3.6–15)	27 (18–35)	43 (32–52)	48 (37–57)
Total	4.1 (2.5–5.7)	9.0 (6.6–11)	18 (15–21)	27 (24–31)	33 (29–37)

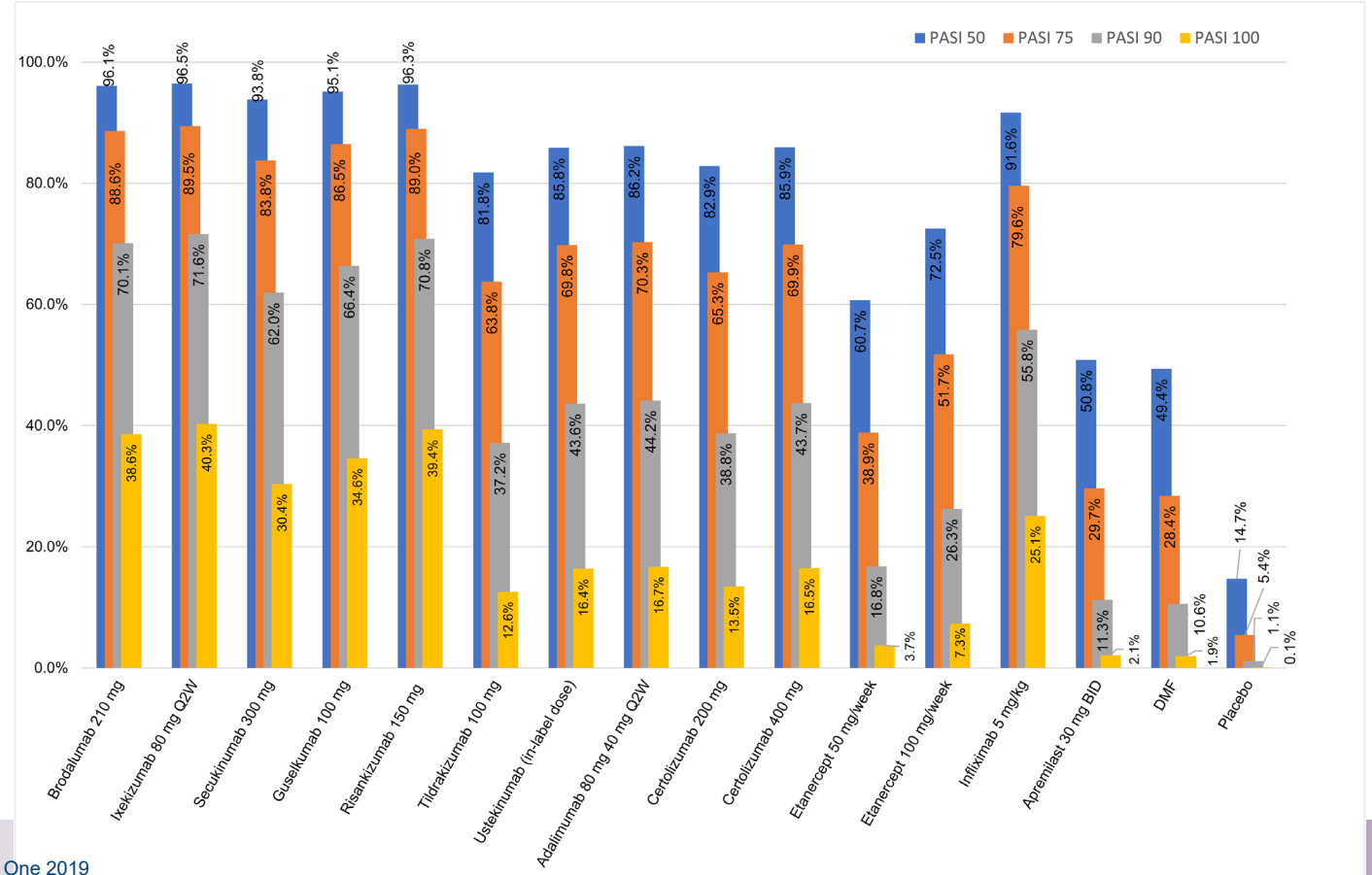


Psoriasis: opgelost?



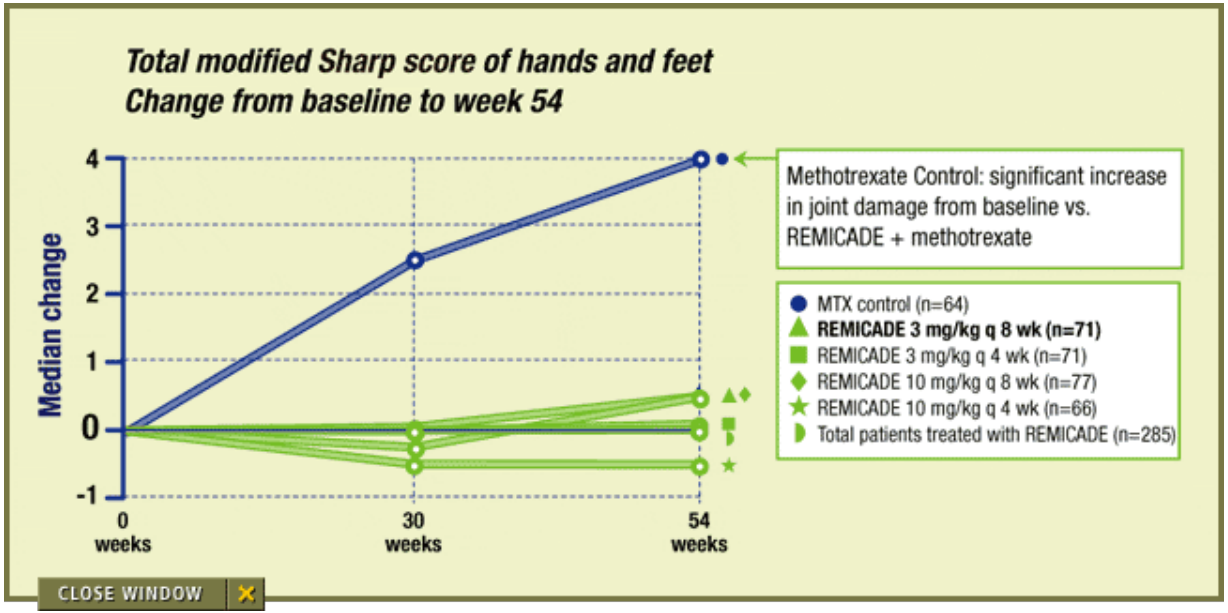
Blaufelt A, JAAD 2017

Op goede weg !



Sawyer LM, Plos One 2019

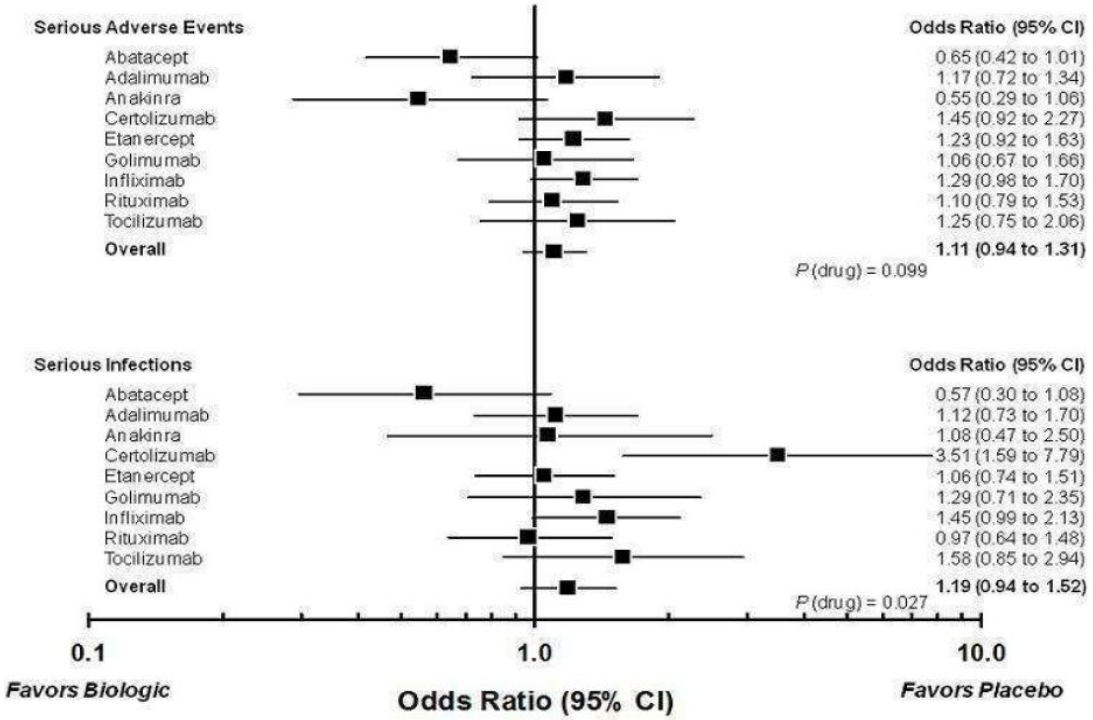
ATTRACT: X-ray scores at 1 year



Lipsky PE, van der Heijde DM, St Clair EW *et al*. N Engl J Med 2000; 343(22):1594-602.

Safety

Serious adverse events or serious infections in a Cochrane review from a meta-analyis: indirect comparisons!!



Auto-antibody induction is not rare
Switching to a lupus phenotype is seen occasionaly under anti-TNF



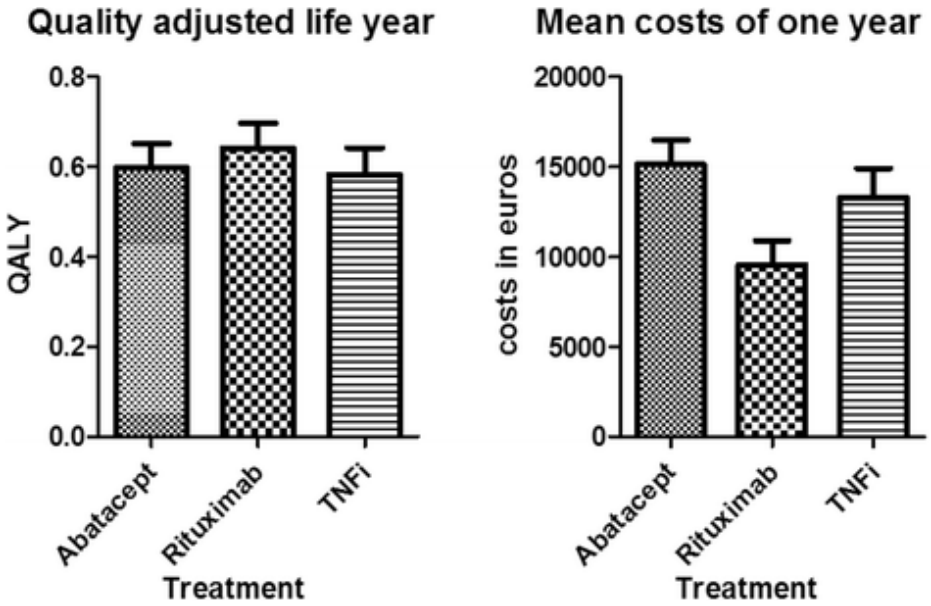
Comorbidities and choice of biologic

Comorbidity	NSAIDs	GCs	HCQ	Sulfasalazine	Methotrexate	Leflunomide	Cyclosporine	Etanercept	Adalimumab	Infliximab	Certolizumab	Golimumab	Ustekinumab
Cardiovascular Disease	C	?											
Congestive Heart Failure	C	C						?	?	?	?	?	
Obesity					C								
Metabolic Syndrome		C			C								
Diabetes		C			C								
Ulcerative Colitis	?			A			OL		A	A		A	
Crohn's Disease	?			A	OL				A	A			A
Uveitis		P						?	P	P			
Osteoporosis		C											
Malignancy								C	C	C	C	C	?
Fatty Liver Disease	C			C	C	C							
Chronic Kidney Disease	C				C	?	SM						
Depression													
Chronic Hepatitis B *	C				C	C		SM	SM	SM	SM	SM	?
Chronic Hepatitis C *	C				C	C		?/P	?	?	?	?	?
HIV								SM	SM	SM	SM	SM	?

A = Approved for primary therapy of the comorbid condition
C = Reason for caution; OL = Off-label use for the therapy of the comorbid condition ;P = Preferred therapy
SM = Requires special monitoring ;? = Data insufficient but concerns have been raised
* When treating patients with chronic infections that can affect the liver, consider consultation with providers having expertise in the area.

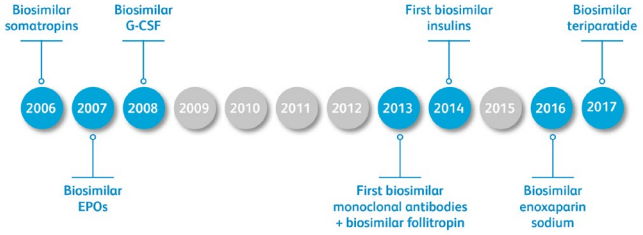
Coates et al, A&R 2016;68(5):1060-71.

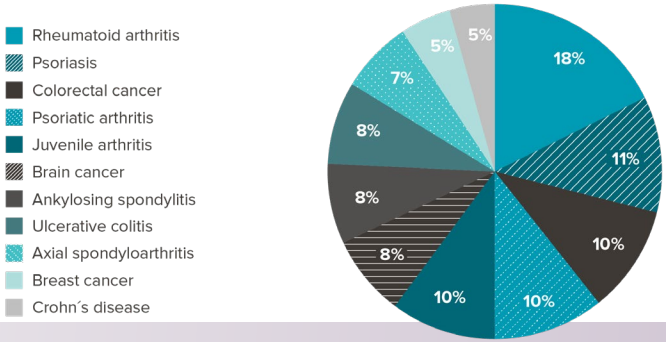
Equal Qualy's ! But different cost

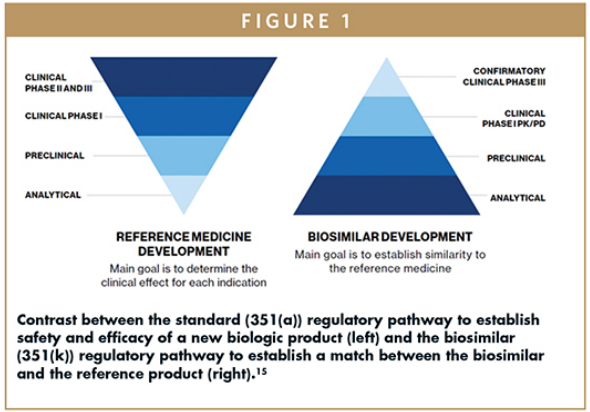


Switching to biosimilars

Biosimilars 2020 in België: friend of foe?







Actief Bestanddeel	Naam	Firma
infliximab	Remicade	MSD
	Inflectra	Hospira
	Remsima	Mundipharma
	Flixabi	biogen
	Zessly	sandoz
etanercept	Enbrel	Pfizer
	Benepali	Biogen
adalimumab	Humira	AbbVie
	Amgevita	Amgen
	Hulio	Mylan
	Hyrimoz	Sandoz
	Idacio	Fresenius Kabi
	Imraldi	Biogen
rituximab	Mabhtera	roche
	Truxima	munidpharma
	Rixathon	sandoz

The future ?

- Dose tapering?
- Withdrawl ?
- Combinations?
- Long Term adverse events
- First line: induction- remission
- Personalised dosage

MIPD software tools for optimal TDM

Current practice

Difficult to dose drug

Non-standard patient





Biomarker concentrations
Drug exposure
Patient characteristics



Dose adjustments based on **trial and error**

Delay in and difficult to reach adequate exposure

Future?

Difficult to dose drug

Non-standard patient





Biomarker concentrations
Drug exposure
Patient characteristics



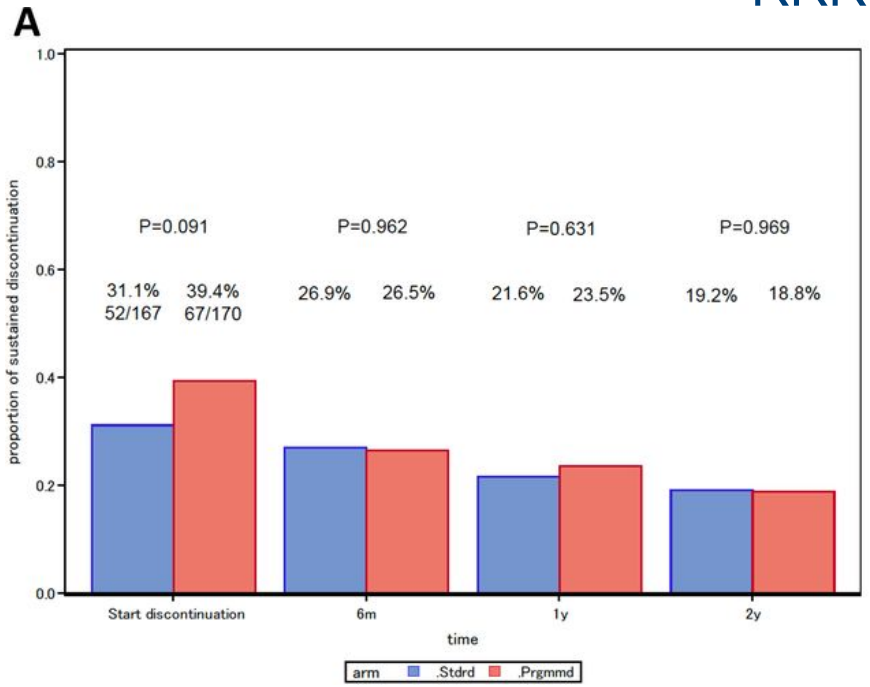
Dose adjustments based on **MIPD software**, using population drug models

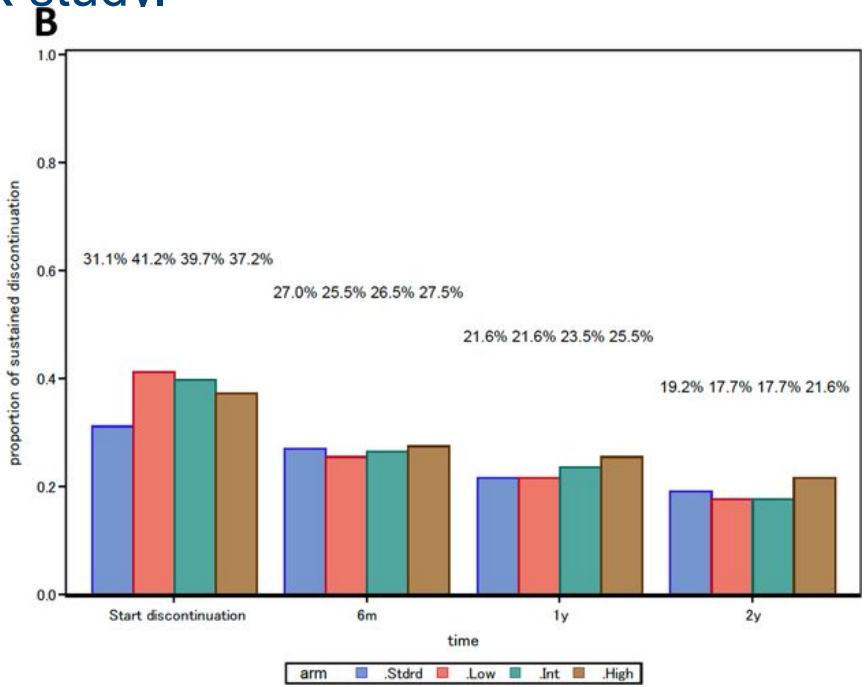
Early and optimal exposure

With the courtesy of Ruth Van Daele, Matthias Gijsen en Erwin Dreesen

Thank you for your attention

Proportions of sustained discontinuation by the standard and programmed treatment group (A) and by the dose of infliximab (B) in patients randomised in RRRR study.





Yoshiya Tanaka et al. Ann Rheum Dis 2020;79:94-102