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UNIVERSITÀ DEGLI STUDI DI MILANO

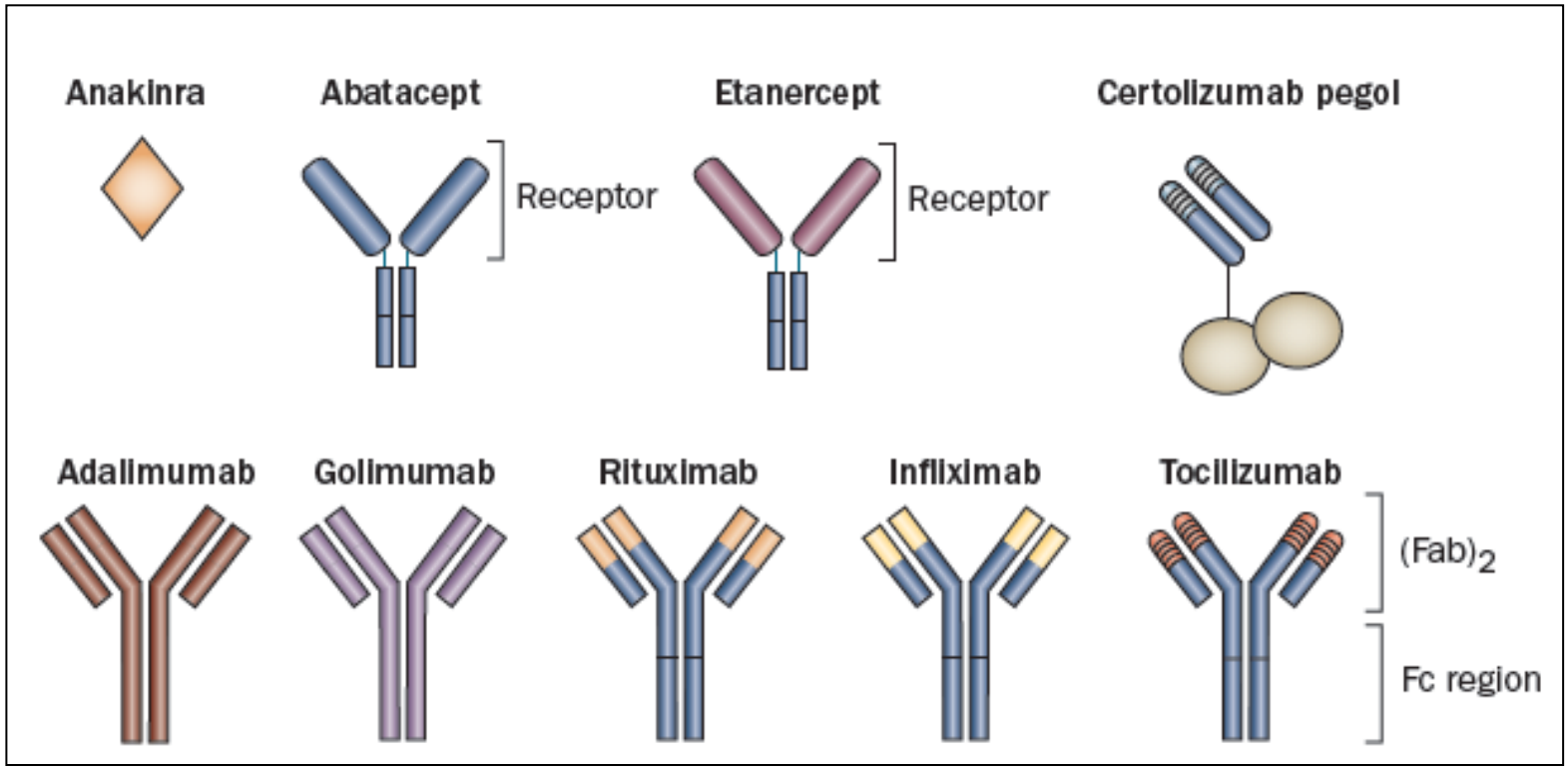
New treatment targets for rheumatoid arthritis

Carlo Selmi
Division of Rheumatology and Clinical Immunology
Humanitas Research Hospital
BIOMETRA Department, University of Milan

Bergamo, 25th June 2016

Current *armamentarium*

Etanercept, infliximab, adalimumab, anakinra, golimumab, certolizumab pegol, rituximab tocilizumab, abatacept (and tofacitinb) are currently approved for the treatment of rheumatoid arthritis.



van Vollenhoven R. Nat Rev Rheumatol 2011

Monoclonal antibodies vs. small molecules

Protein-based therapeutics interrupt the two fundamental mechanisms for immunological communication, ***blocking cytokines and cognate cell-cell interaction.***

Small molecule therapeutics is based not on the blockade of extracellular communication, but on the ***interruption of intracellular signalling*** based on the inhibition of kinases. By interrupting one or more kinases it is possible to modulate the function of cellular structures such as surface receptors, signalling proteins and transcription of nuclear proteins, thus influencing the behaviour of the cell types targeted.

Kelly V, Genovese M. Rheumatology 2013

Outline

1 Yesterday: anti-TNFα

2 **Today**

Cytokines

Intracellular signalling

Biosimilars

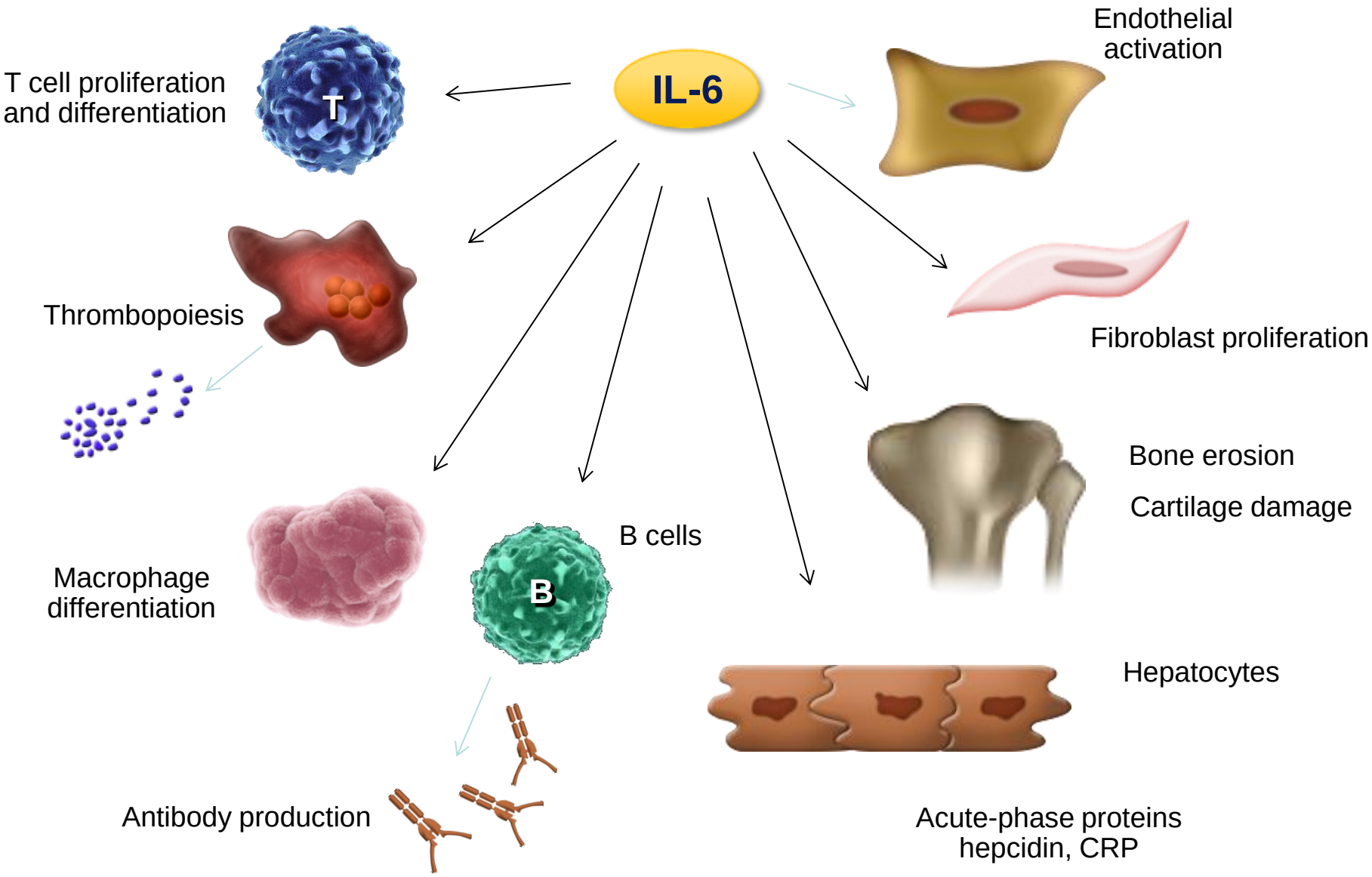
3 **Tomorrow**

New pathways for intervention: B cells and chemokines

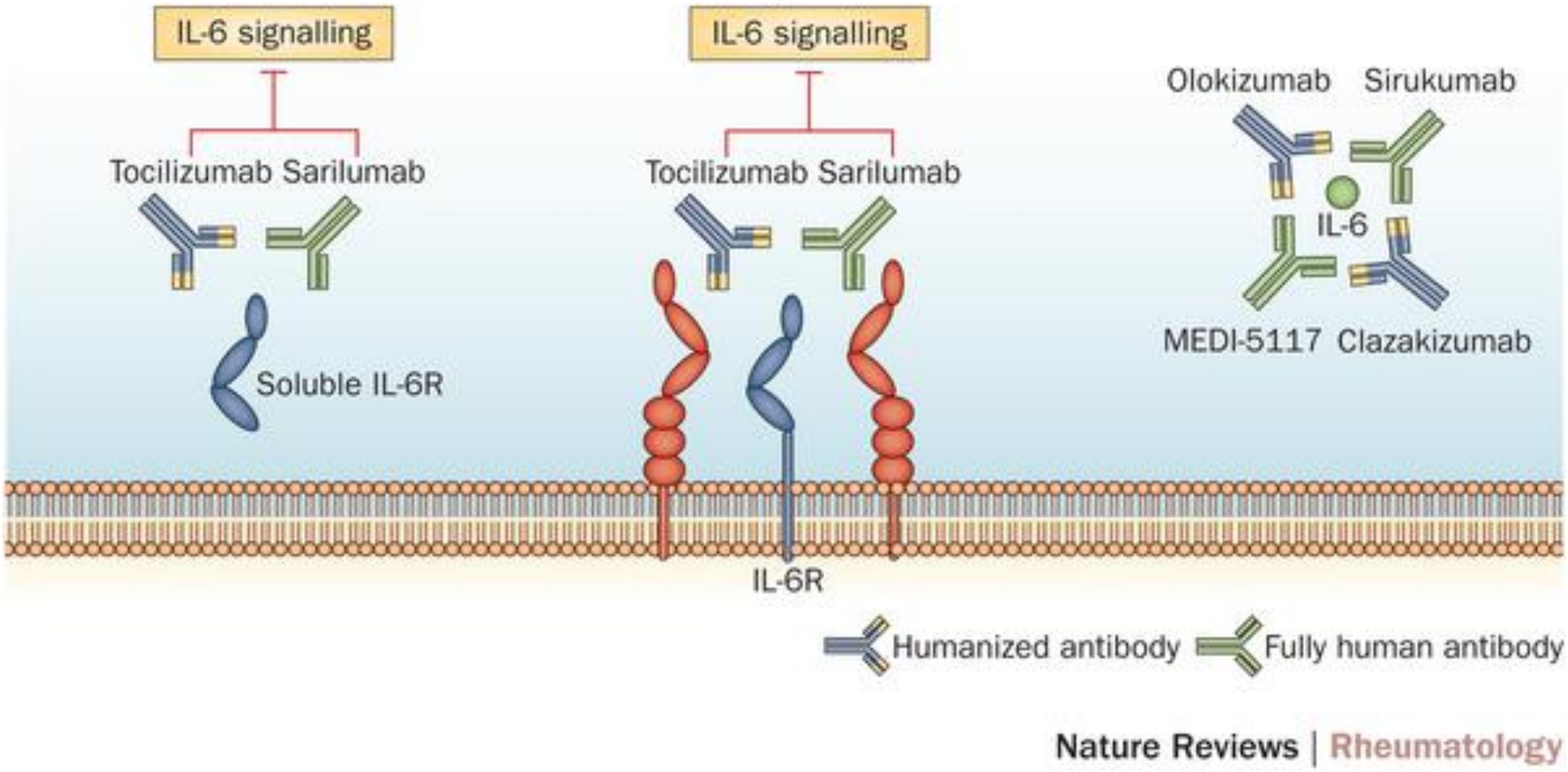
New treatment strategies with old drugs

Nanoparticles?

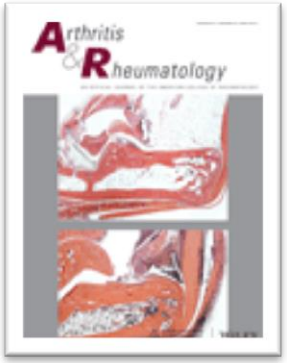
The new clothes of IL6



McInnes IB, et al. *Nature Rev Immunol*. 2007; Kishimoto T. *Arthritis Res Ther* 2006



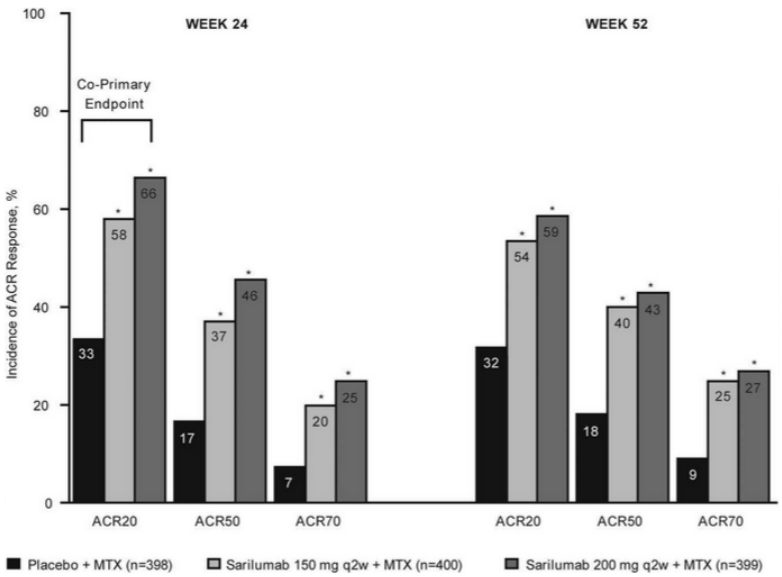
Ruderman EM Nat Rev Rheumatol 2015

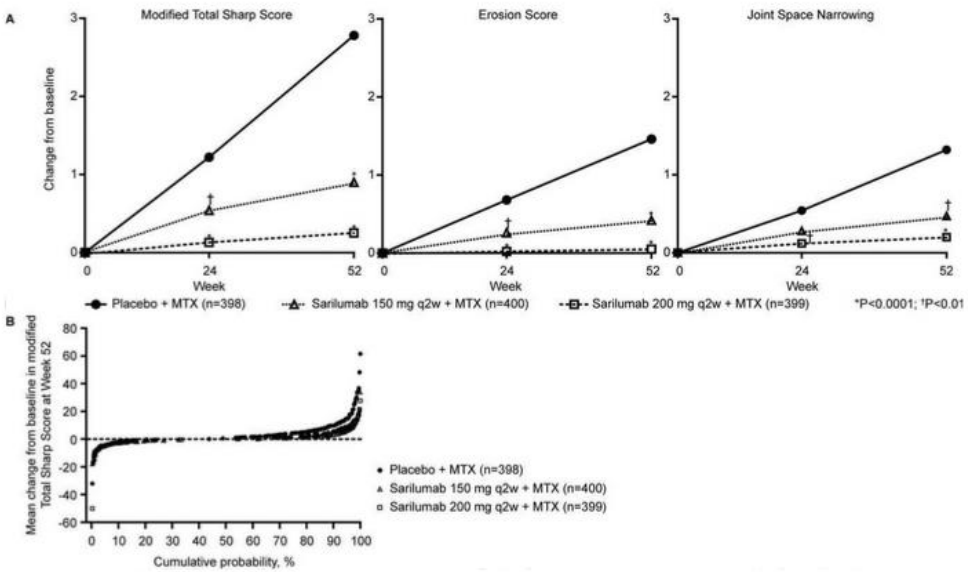


Sarilumab

In RA patients treated with sarilumab (150 mg or 200 mg every 2 weeks) in combination with MTX, both doses provided sustained clinical efficacy, as shown by significant improvements in symptomatic, functional, and radiographic outcomes.

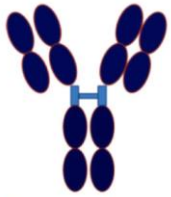
Sarilumab was generally well tolerated.

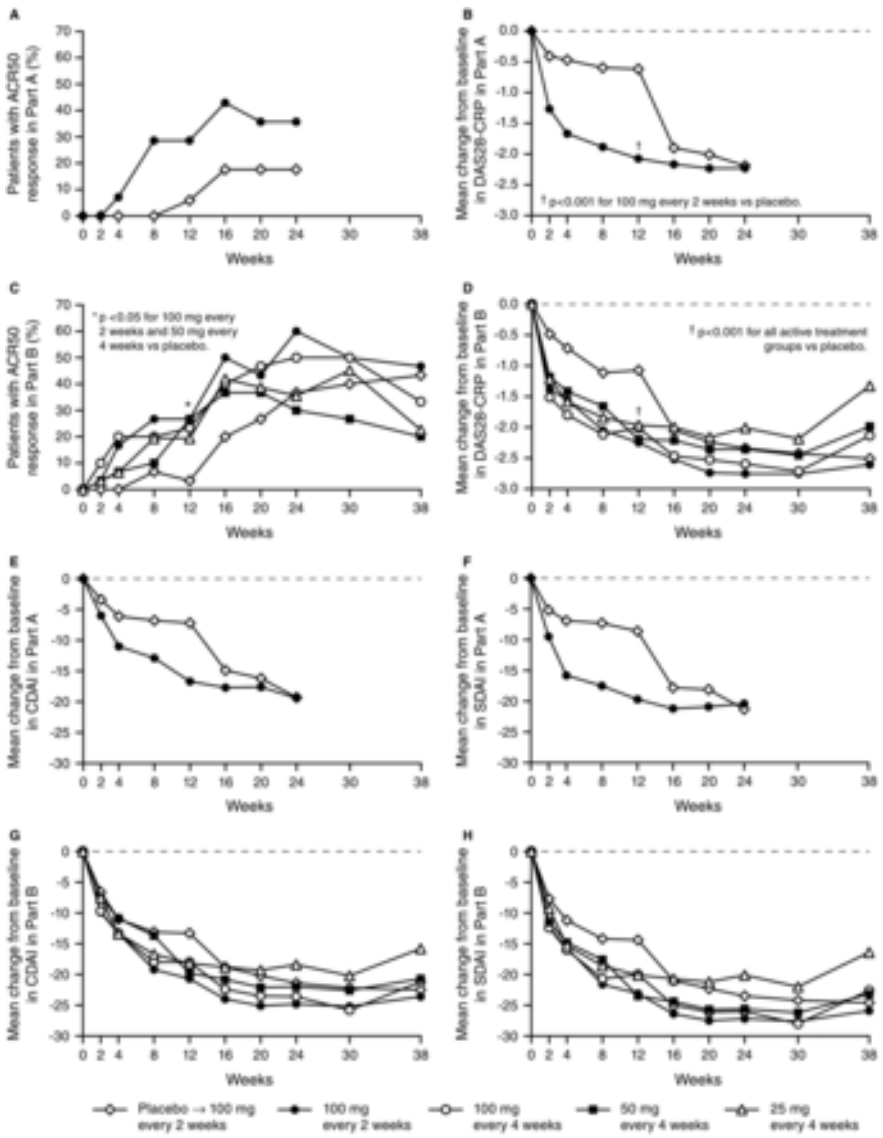




Genovese MC. *et al*. Arthritis Rheumatol 2015.

Sirukumab





EXTENDED REPORT

Sirukumab, a human anti-interleukin-6 monoclonal antibody: a randomised, 2-part (proof-of-concept and dose-finding), phase II study in patients with active rheumatoid arthritis despite methotrexate therapy

Josef S Smolen,[1,2] Michael E Weinblatt,[3] Shihong Sheng,[4] Yanli Zhuang,[5] Benjamin Hsu[6]

Sirukumab-treated patients experienced improvements in the signs/symptoms of RA

A clinical trial to compare sirukumab and adalimumab monotherapy is being organized

Smolen JS. *et al*. Ann Rheum Dis 2014

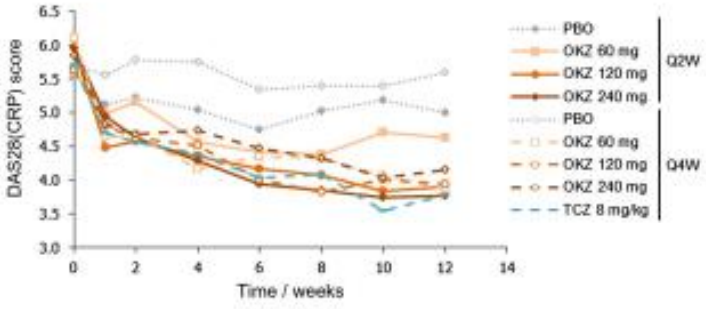
Olokizumab

EXTENDED REPORT

Efficacy and safety of olokizumab in patients with rheumatoid arthritis with an inadequate response to TNF inhibitor therapy: outcomes of a randomised Phase IIb study

Mark C Genovese,[1] Roy Fleischmann,[2] Daniel Furst,[3] Namieta Janssen,[4] John Carter,[5] Bhaskar Dasgupta,[6] Judy Bryson,[7] Benjamin Duncan,[7] Wei Zhu,[7] Costantino Pitzalis,[8] Patrick Durez,[9] Kosmas Kretsos[10]

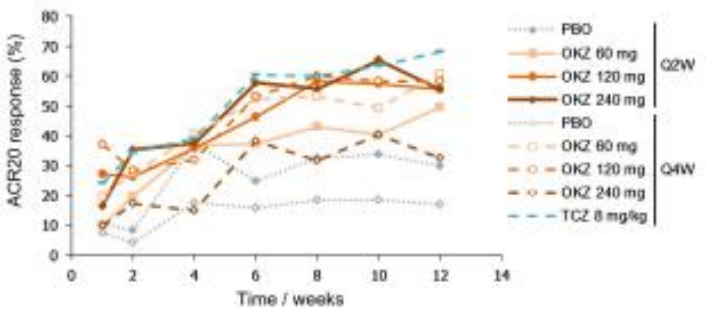
A



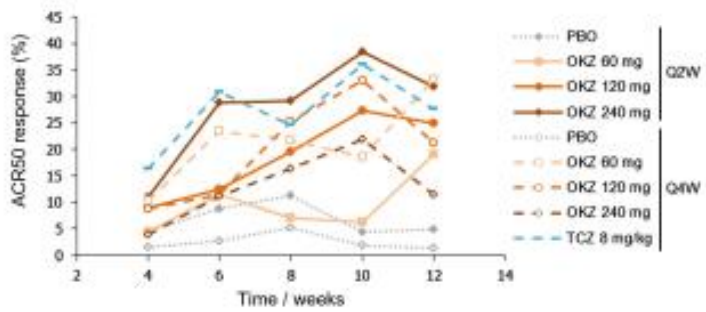
B

Dosing Frequency	Statistic	PBO	OKZ 60 mg	OKZ 120 mg	OKZ 240 mg	p-value[b]
Q4W	N	22	22	23	22	
	n	20	15	18	21	
	Mean (SD)	-0.11 (1.23)	-2.29 (1.37)	-1.77 (1.23)	-1.70 (0.82)	
	Median	0.02	-1.97	-1.84	-1.84	
	Min, max	-2.6, 2.1	-6.0, -0.2	-3.8, 0.2	-3.2, -0.1	
	LS Mean (SE)	-0.15 (0.25)	-1.85 (0.28)	-1.86 (0.26)	-1.62 (0.25)	
Q2W	N	22	20	22	23	
	n	21	17	20	21	
	Mean (SD)	-0.67 (1.30)	-1.18 (0.99)	-1.96 (1.35)	-2.06 (1.28)	
	Median	-0.66	-1.12	-1.80	-2.15	
	Min, max	-3.9, 1.9	-3.1, 0.5	-4.4, 0.9	-5.5, -0.1	
	LS Mean (SE)	-0.79 (0.25)	-1.16 (0.27)	-1.89 (0.25)	-2.02 (0.25)	
						<0.0001

C

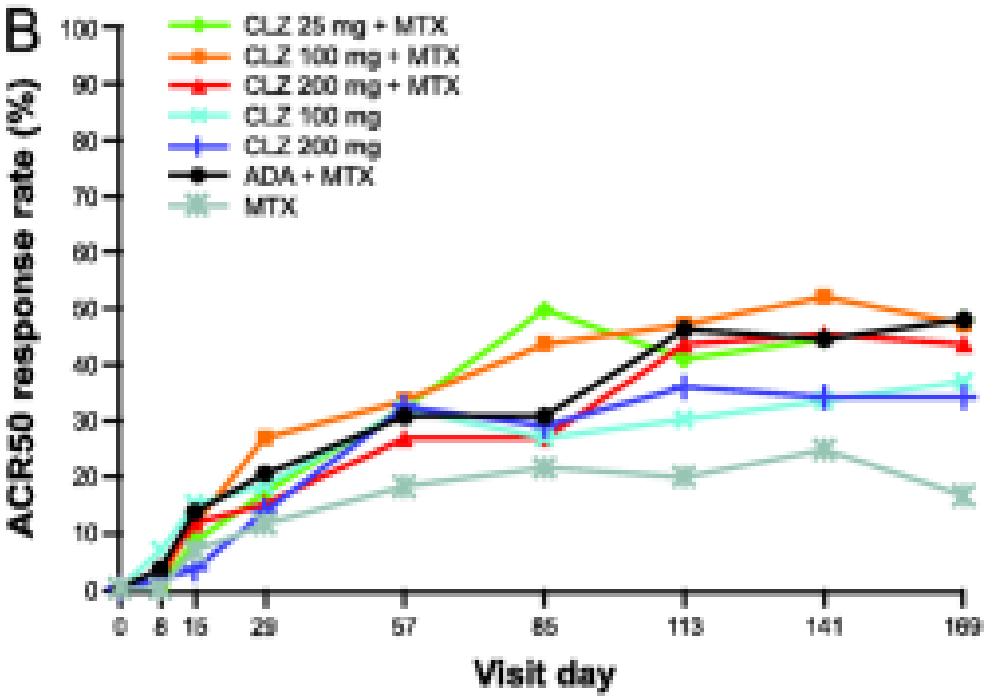


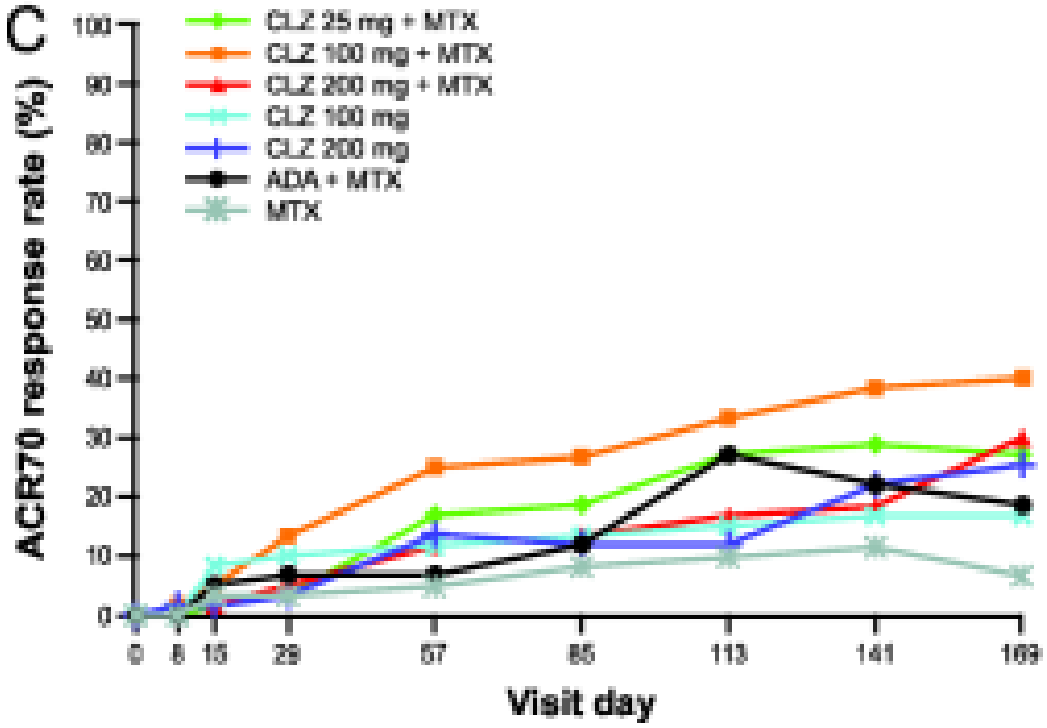
D



Genovese MC. *et al*. Ann Rheum Dis 2014

Clazakizumab





Weiblatt ME. *et al*. Arthitis Rheumatol 2015

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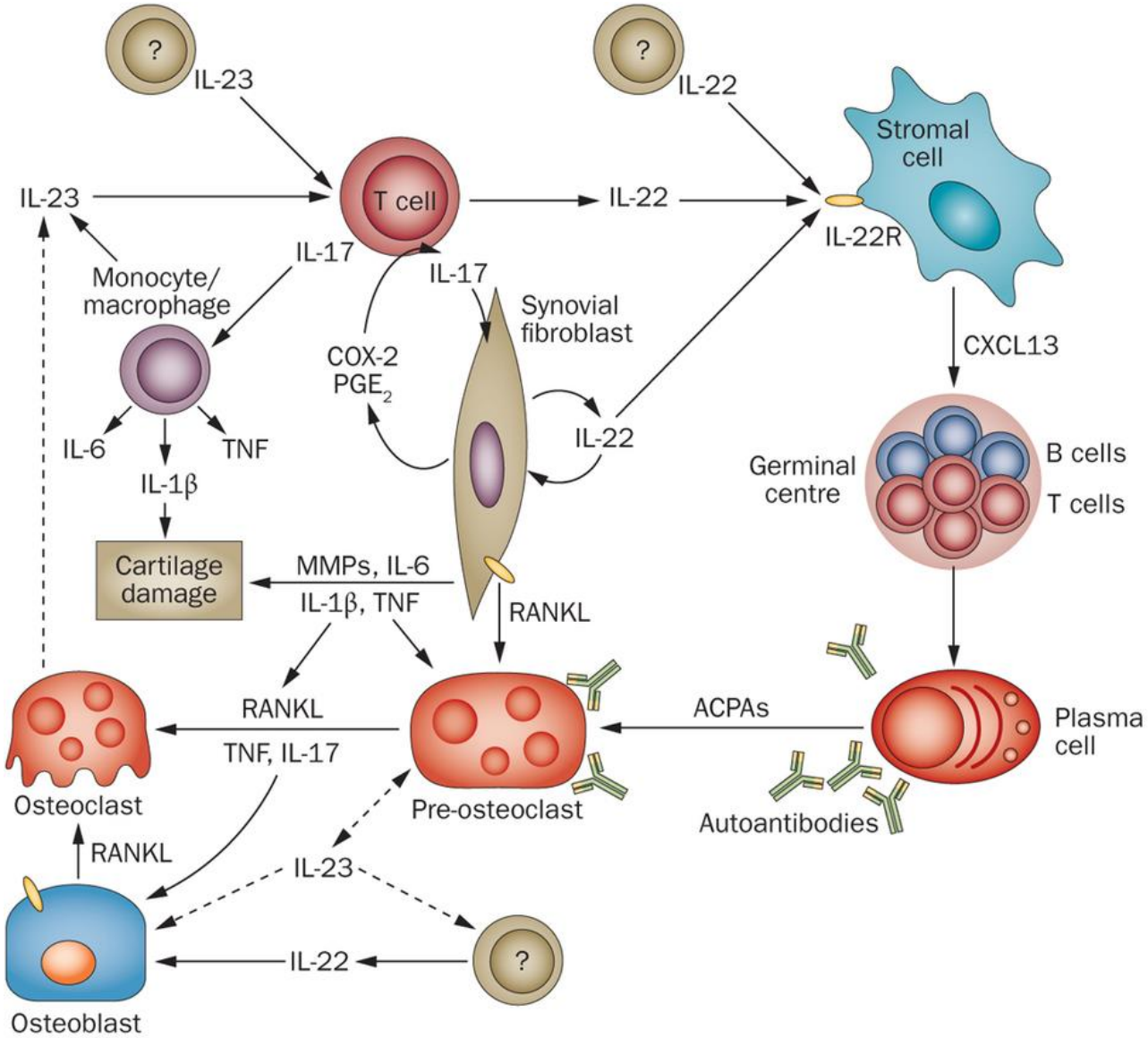
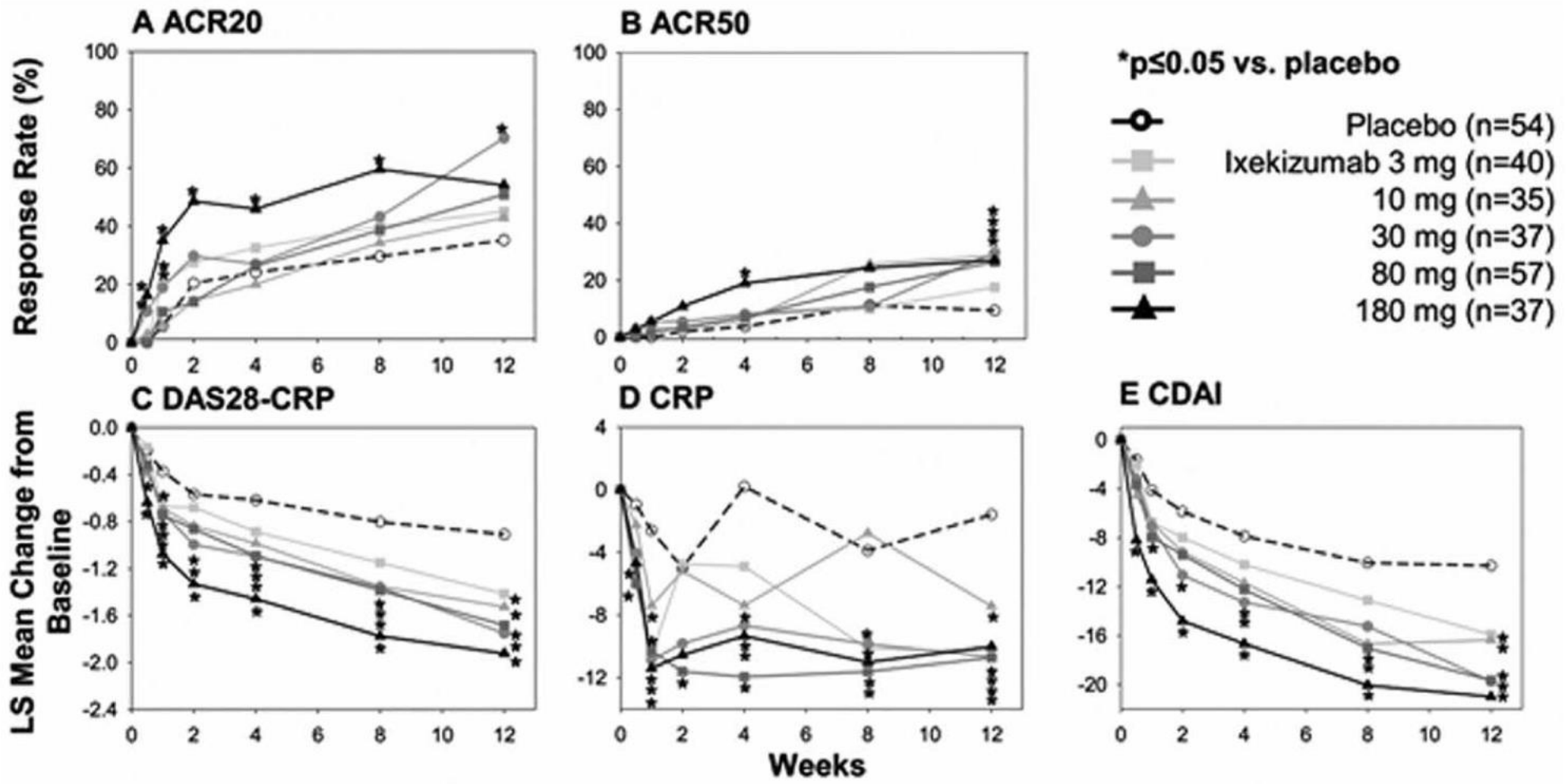


Nature Reviews | Rheumatology

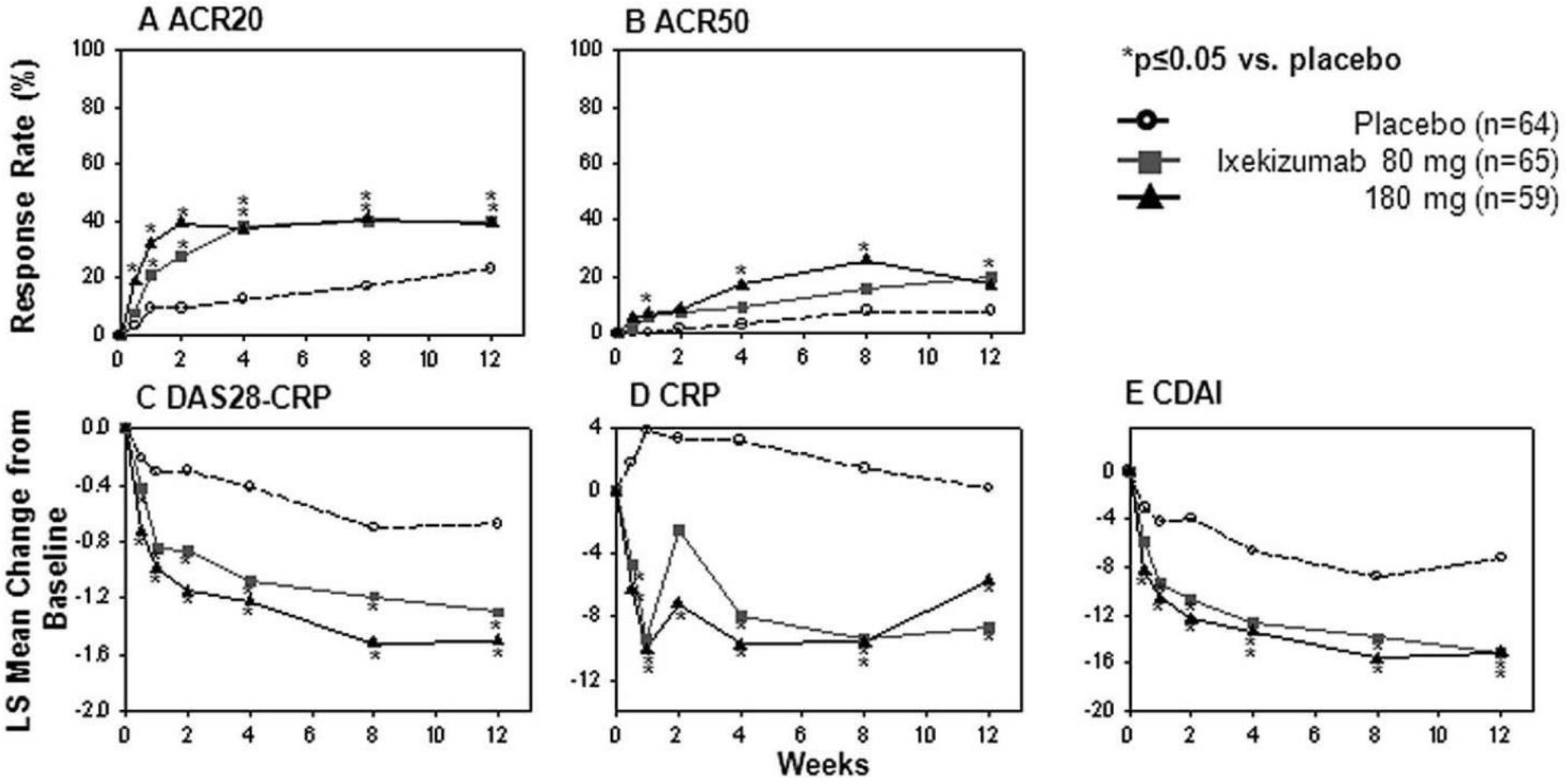
Lubberts E, Nat Rev Rheumatol 2015

Ixekizumab-Phase II
Biologics naive



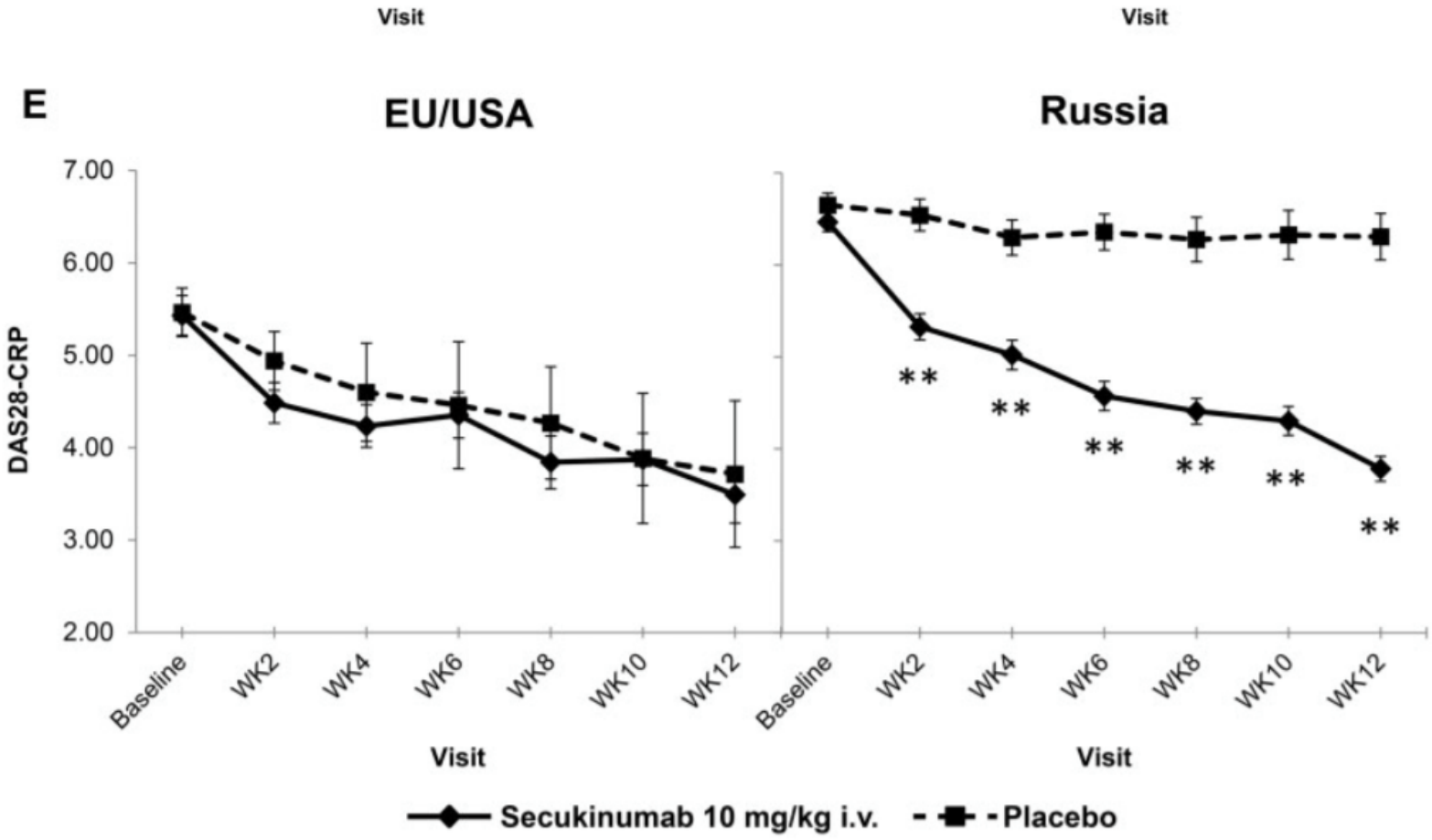
Genovese MC, Arthritis Rheum 2014

Ixekizumab-Phase II
TNF inadequate responders



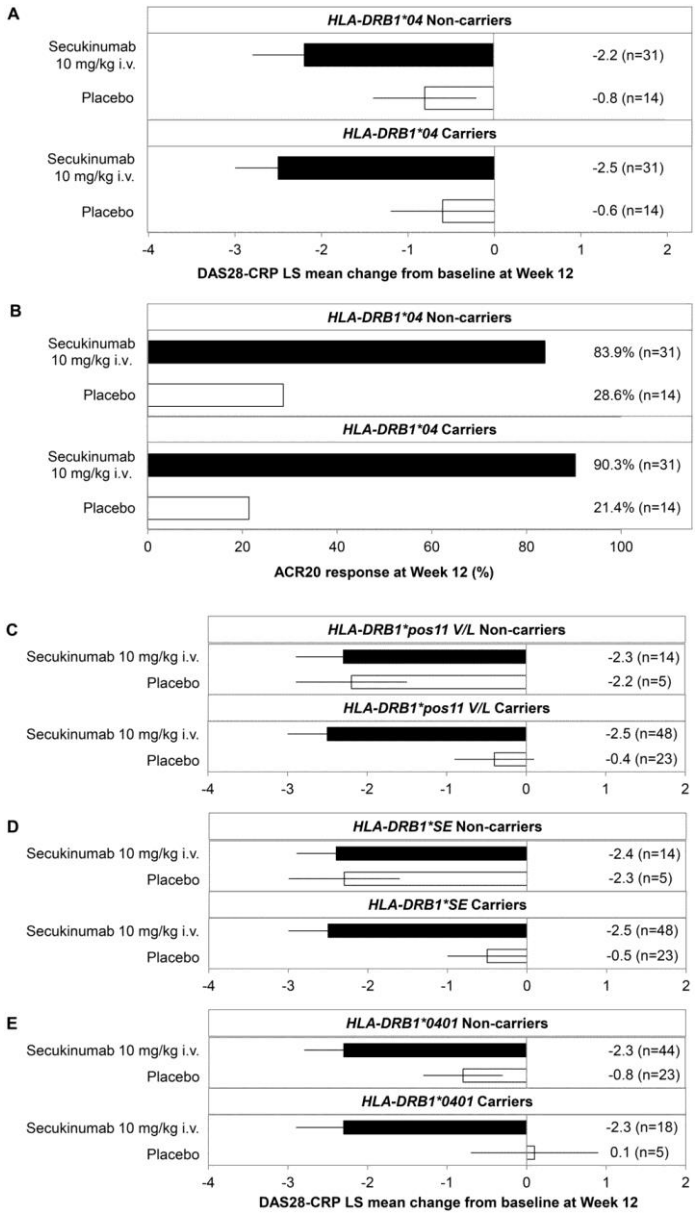
Genovese MC, Arthritis Rheum 2014

Secukinumab
Regional variations



Burmester GR, Rheumatology (Oxford). 2016

Secukinumab
Biomarkers



Burmester GR, Rheumatology (Oxford). 2016

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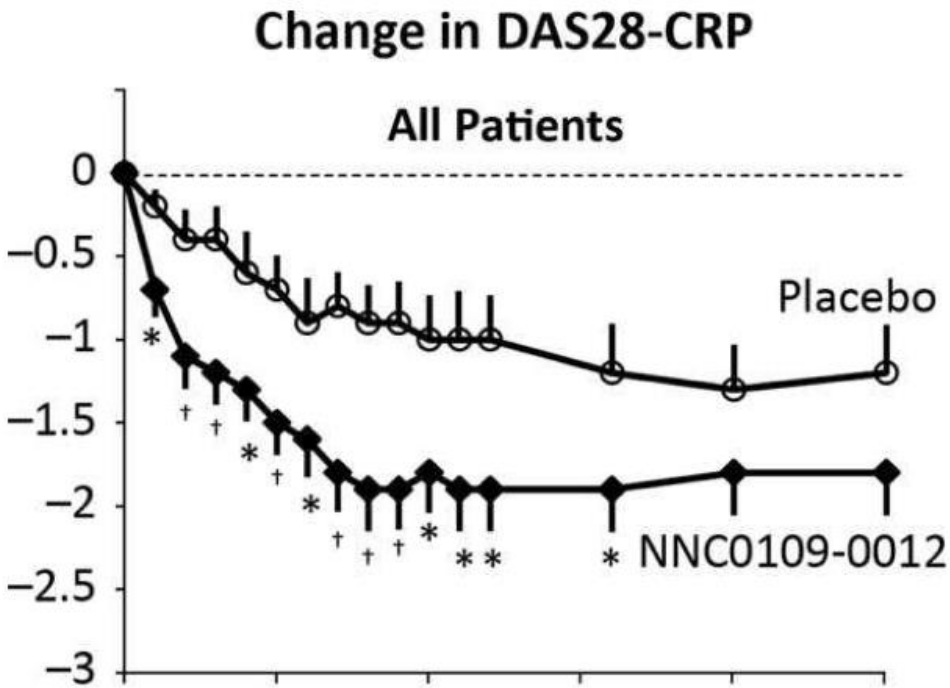

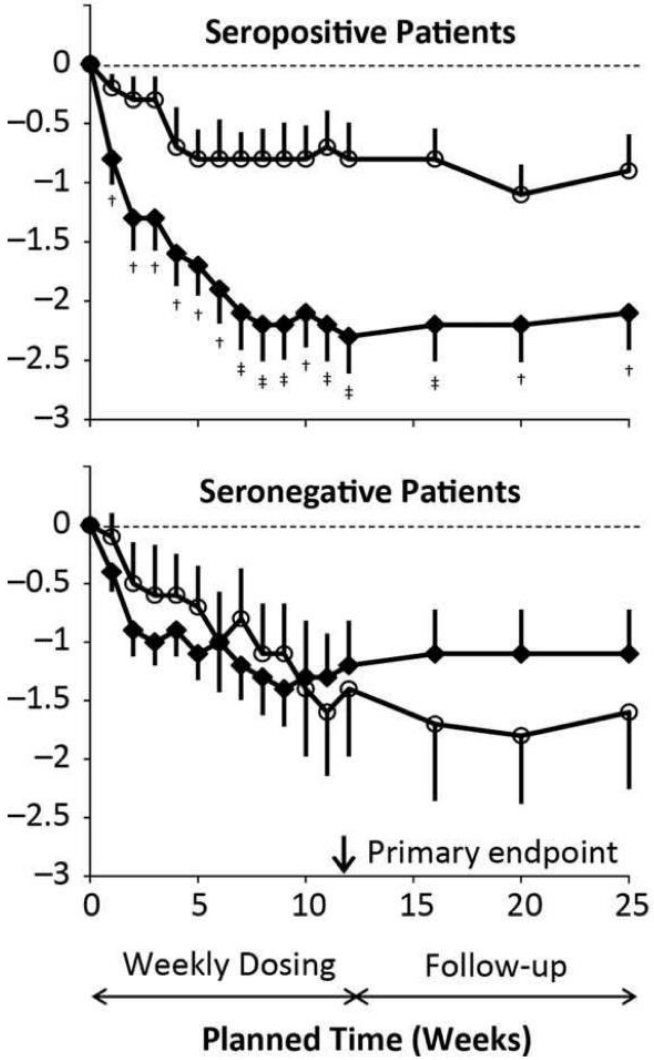

Senolt L et al, Arthr Rheumatol 2015

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Cytokines

Intracellular signalling

Biosimilars

3 **Tomorrow**

New pathways for intervention: B cells and chemokines

New treatment strategies with old drugs

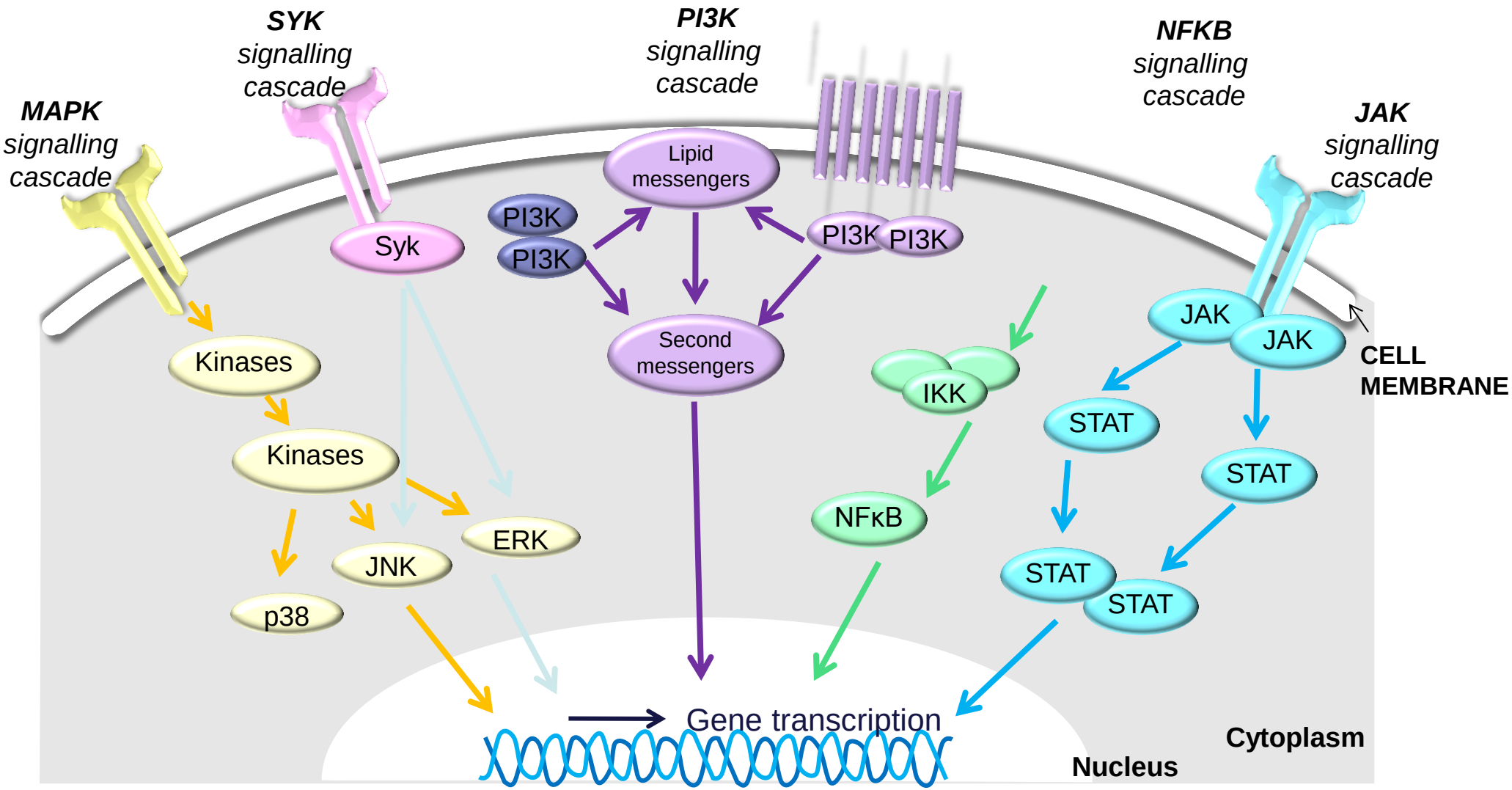
Nanoparticles?

Targeting small molecules

- **Inhibitors of the JAK-STAT signaling pathway**
- Syk kinase inhibitors
- Phosphodiesterase-4 inhibitors
- MAPK p38 inhibitors

Jacques P, Van den Bosch F. Expert Opin Emerging Drugs 2013

Cytokines Signal Through Different Intracellular Pathways



Adapted from Mavers M, et al. *Curr Rheum Rep*. 2009;11:378-385 and Rommel C, et al. *Nat Rev Immunol.* 2007;7:191-201.

Tofacitinib (CP-690,550) in Patients With Rheumatoid Arthritis Receiving Methotrexate

Twelve-Month Data From a Twenty-Four–Month Phase III Randomized Radiographic Study

Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 9, 2012 VOL. 367 NO. 6

Placebo-Controlled Trial of Tofacitinib Monotherapy in Rheumatoid Arthritis

RESEARCH ARTICLE Open Access

Efficacy, safety and tolerability of tofacitinib in patients with an inadequate response to disease modifying anti-rheumatic drugs: a meta-analysis of randomized double-blind controlled studies

ACR 20

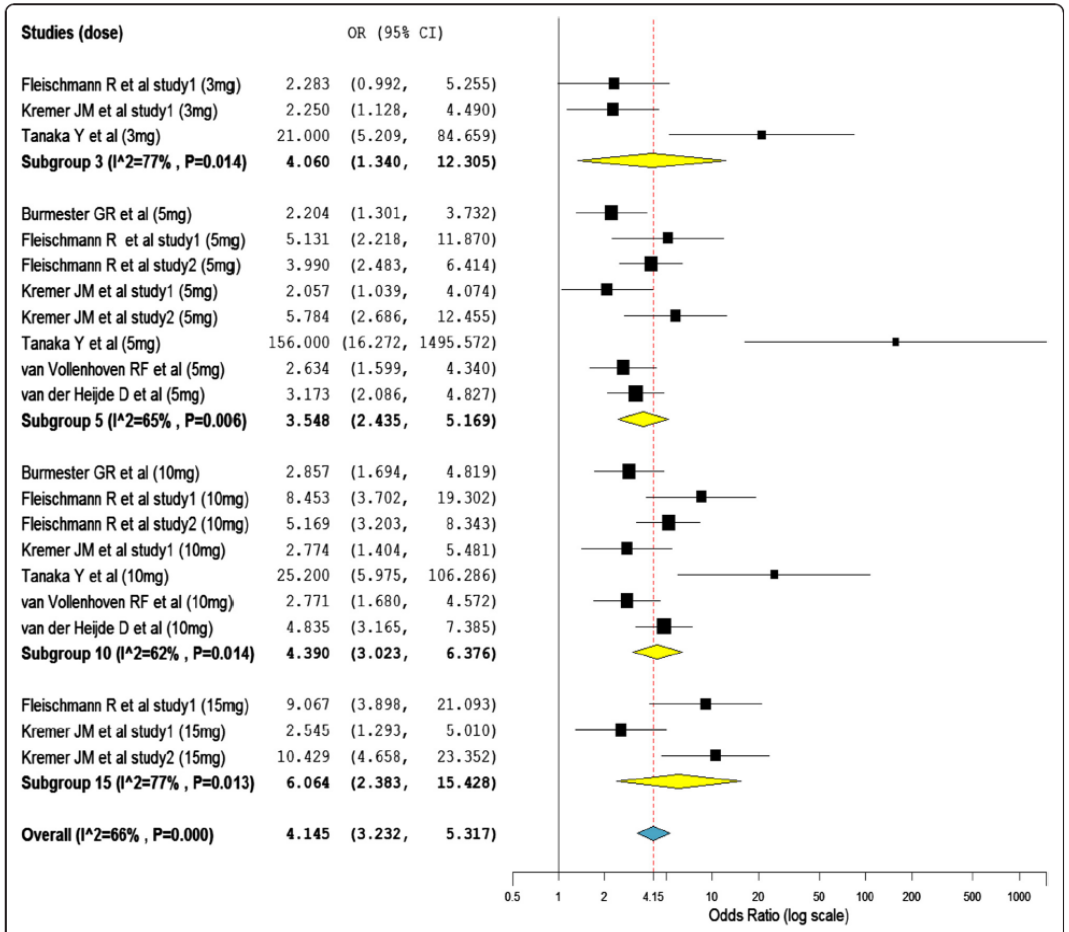


Figure 2 Mantel-Haenszel odds ratio of at least a 20% improvement in the American College of Rheumatology scale (ACR 20).

HAQ-DI

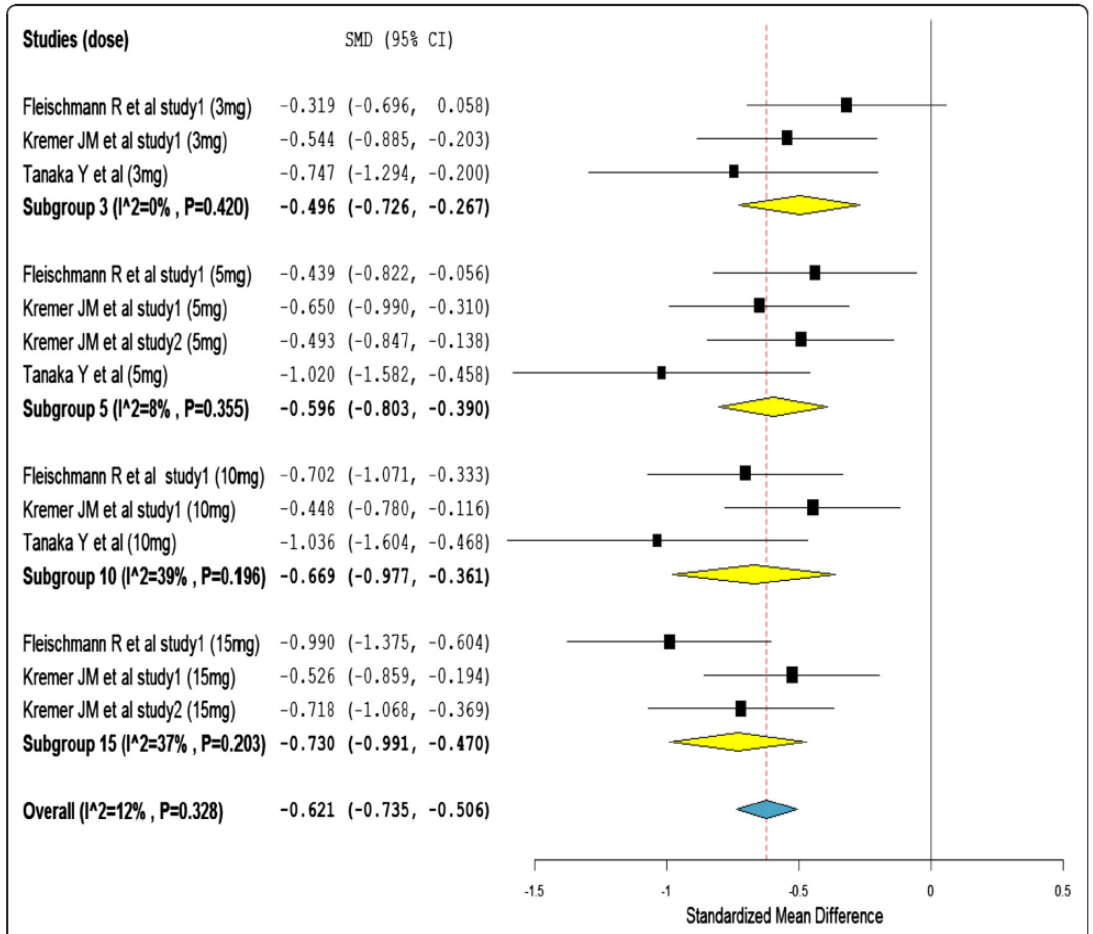


Figure 3 Standardize mean difference of change in the Health Assessment Questionnaire–Disability Index (HAQ DI) scores.

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Behran A. BMC Musculoskel Dis 2013

RESEARCH ARTICLE Open Access

Efficacy, safety and tolerability of tofacitinib in patients with an inadequate response to disease modifying anti-rheumatic drugs: a meta-analysis of randomized double-blind controlled studies

Infections

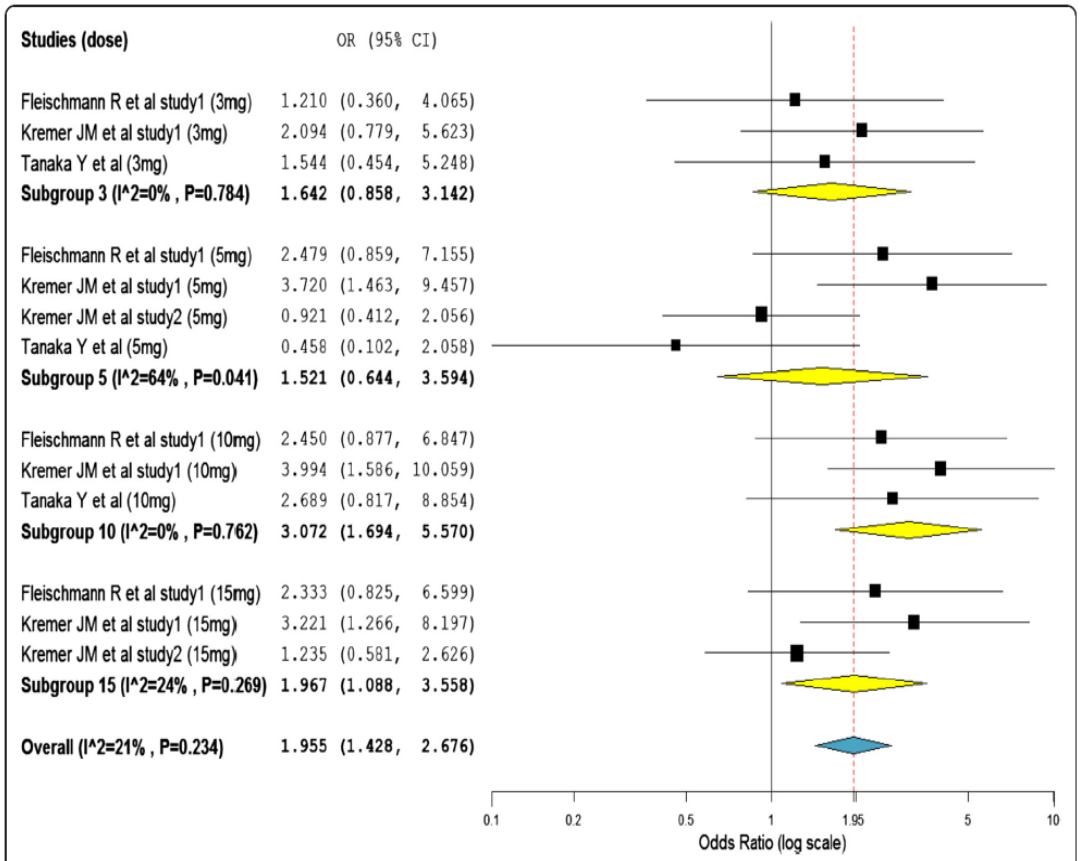

Figure 4 Mantel-Haenszel odds ratio of patients reporting treatment emergent infections.

Patients discontinued due to AE

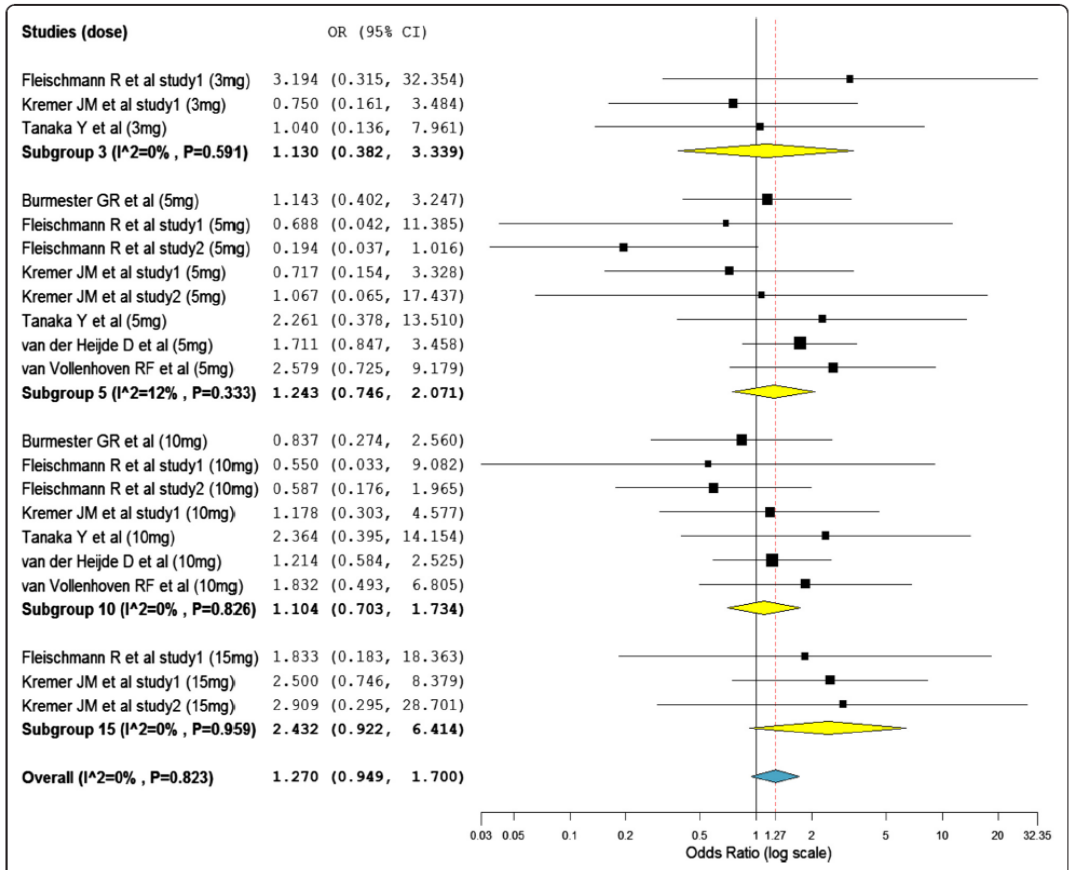

Figure 6 Mantel-Haenszel odds ratio of patients who discontinued the treatment due to treatment-emergent adverse events.

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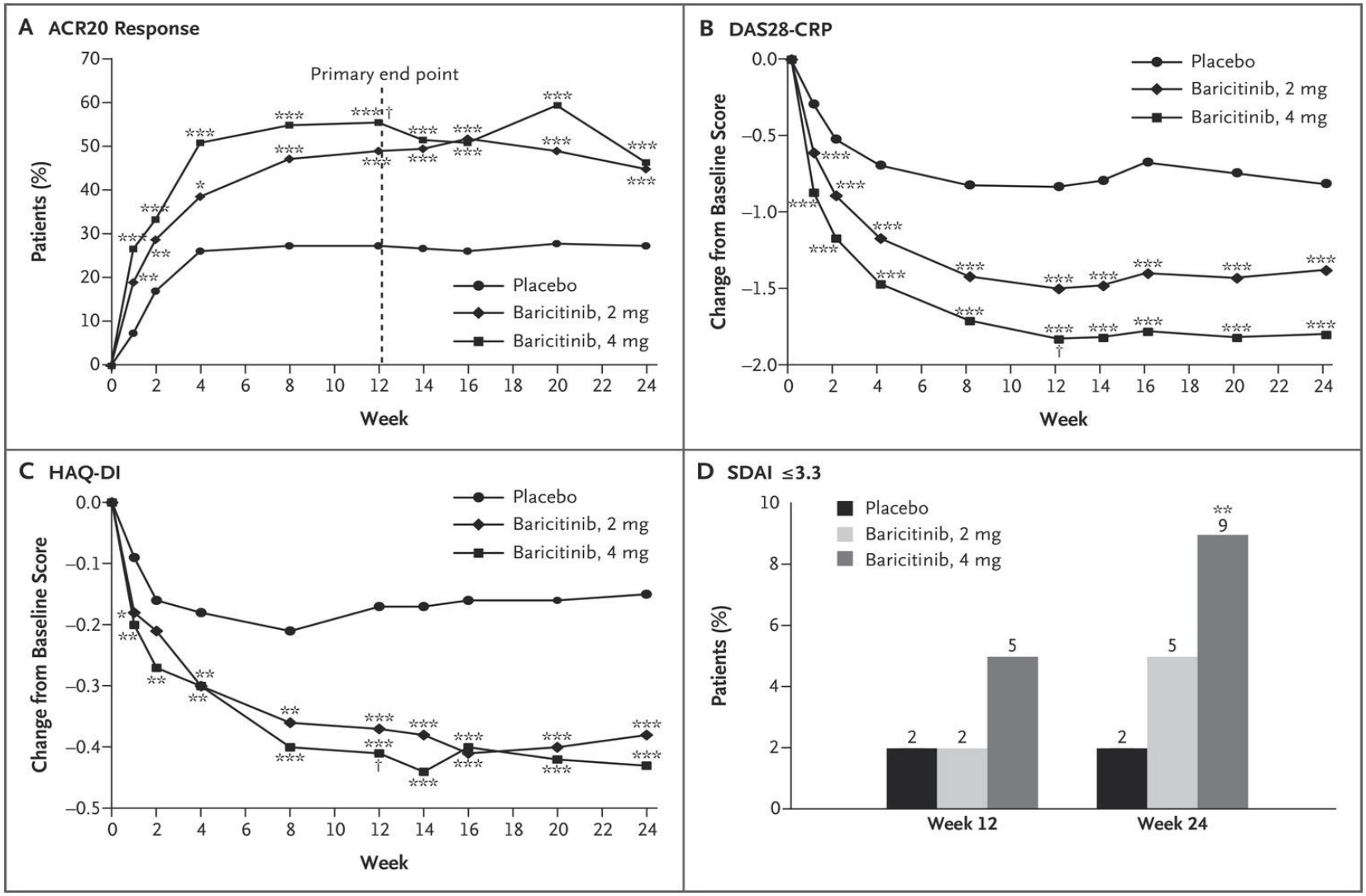
Behran A. BMC Musculoskel Dis 2013

What about other JAK inhibitors?

	Target	Status for RA	Lymphocyte count	Compared to biologics		Clinical efficacy	
				Malignancy	Herpes zoster	Versus MTX	Versus TNF
Tofacitinib	JAK1/3	FDA approved	↓	→	↑	↑	→
Baricitinib	JAK1/2	Phase III	→	?	↑	↑	↑
Peficitinib	JAK1/3	Phase II	→	?	?	?	?
Decernotinib	JAK3	Phase II	↓	?	?	?	?
Filgotinib	JAK1	Phase II	→	?	?	?	?
ABT-494	JAK1	Phase II	→	?	?	?	?
NIP-565	JAK1	Preclinical	?	?	?	?	?

Yamaoka K Curr Opin Chem Biol 2016

Baricitinib
RA-BEACON



Genovese MC, et al. NEJM. 2016

Peficitinib

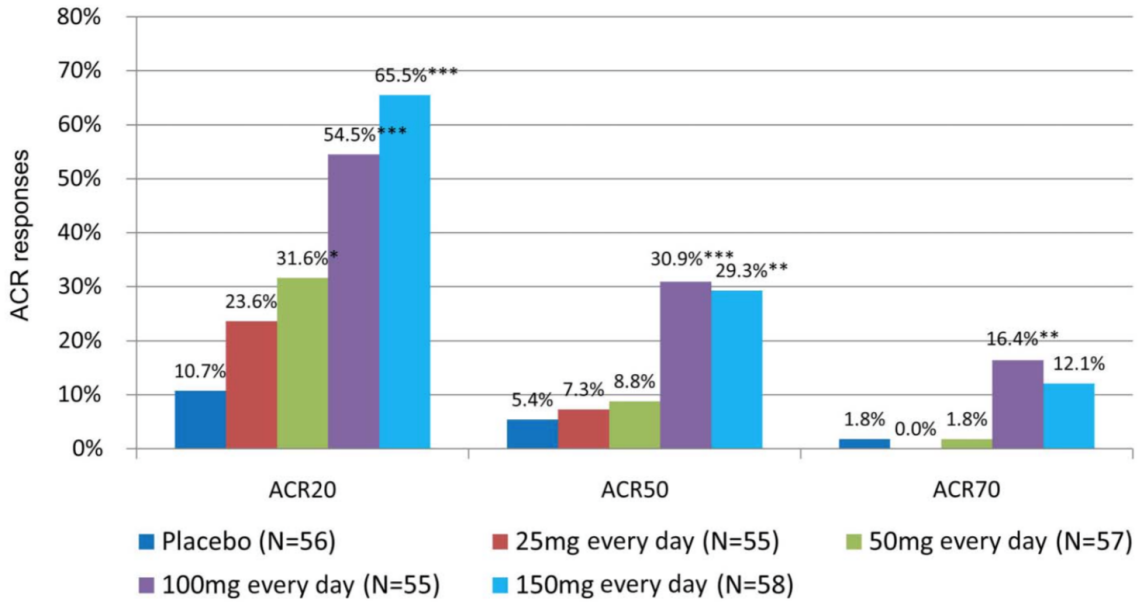
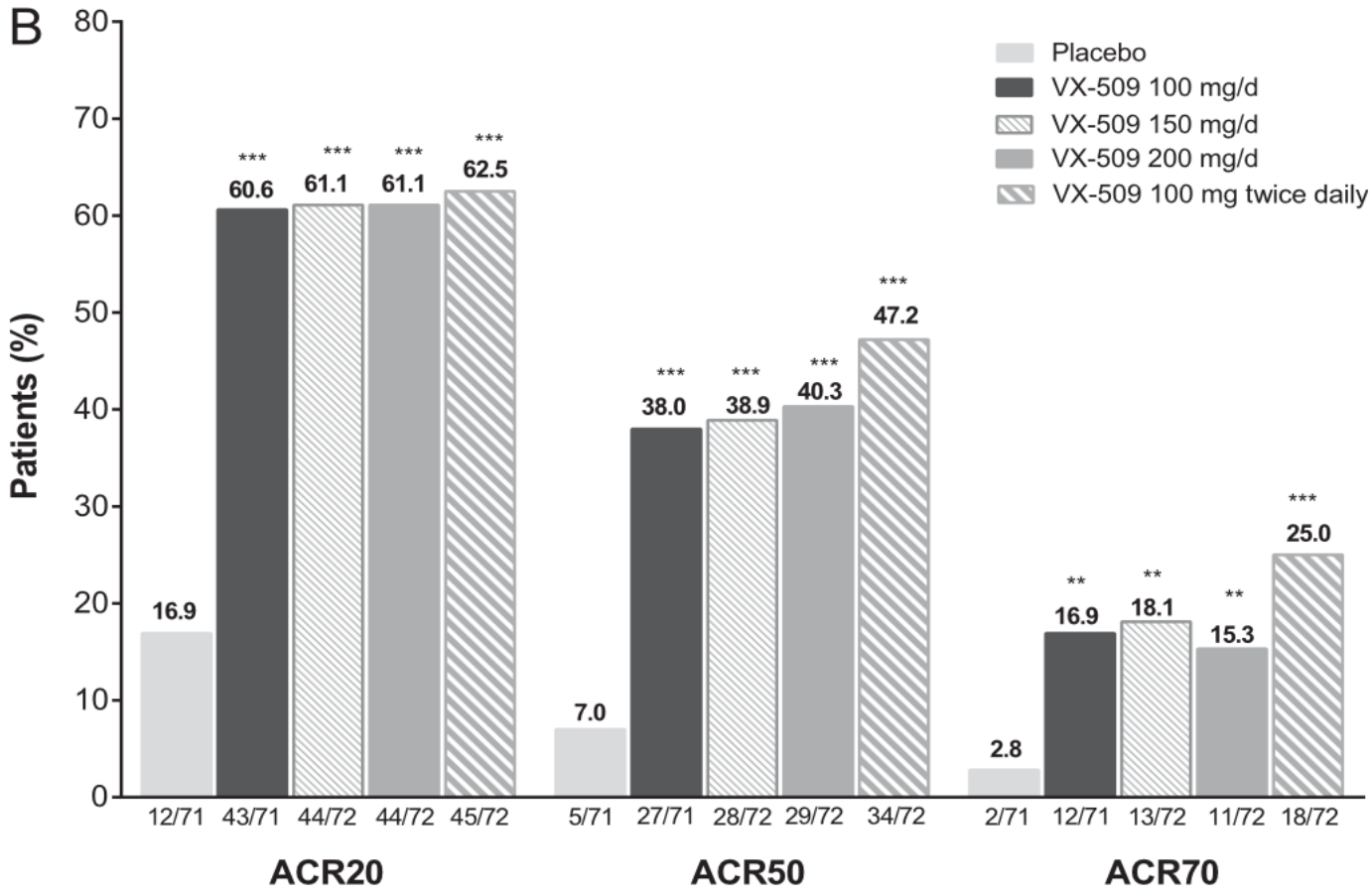


Table 2 Overview of TEAEs

	Placebo (N=56)	Peficitinib 25 mg (N=55)	Peficitinib 50 mg (N=57)	Peficitinib 100 mg (N=55)	Peficitinib 150 mg (N=58)	Peficitinib total (N=225)
Any TEAEs	36 (64.3%)	39 (70.9%)	37 (64.9%)	29 (52.7%)	39 (67.2%)	144 (64.0%)
≥Grade 3 TEAEs*	3 (5.4%)	4 (7.3%)	3 (5.3%)	6 (10.9%)	2 (3.4%)	15 (6.7%)
Serious TEAEs	1 (1.8%)	1 (1.8%)	2 (3.5%)	3 (5.5%)	0	6 (2.7%)
Deaths	0	0	1 (1.8%)	0	0	1 (0.4%)
TEAEs leading to discontinuation	10 (17.9%)	7 (12.7%)	5 (8.8%)	6 (10.9%)	4 (6.9%)	22 (9.8%)
Infections and infestations	12 (21.4%)	18 (32.7%)	14 (24.6%)	7 (12.7%)	17 (29.3%)	56 (24.9%)
GI disorders	3 (5.4%)	8 (14.5%)	11 (19.3%)	6 (10.9%)	10 (17.2%)	35 (15.6%)

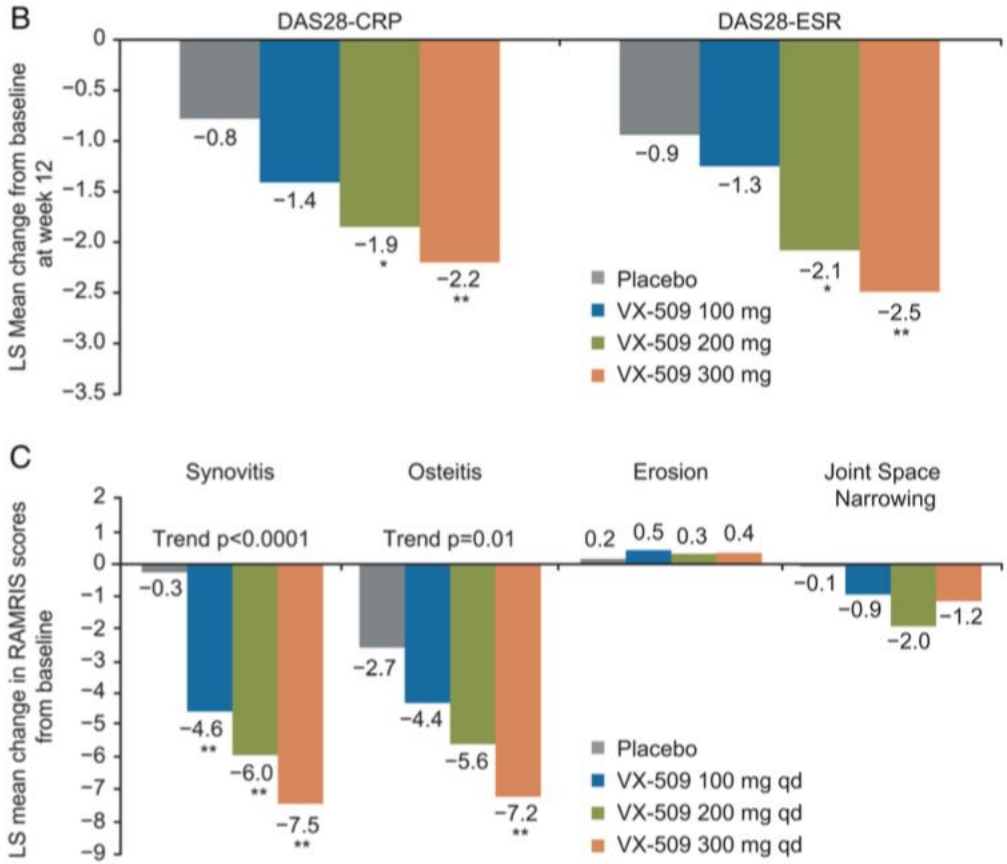
Takeuchi T, et al. Ann Rheum Dis. 2016

VX-509 (Decernotinib), an Oral Selective JAK-3 Inhibitor, in Combination With Methotrexate in Patients With Rheumatoid Arthritis



Genovese MC, et al. Arthritis Rheumatol. 2016

Efficacy of VX-509 (decernotinib) in combination with a disease-modifying antirheumatic drug in patients with rheumatoid arthritis: clinical and MRI findings



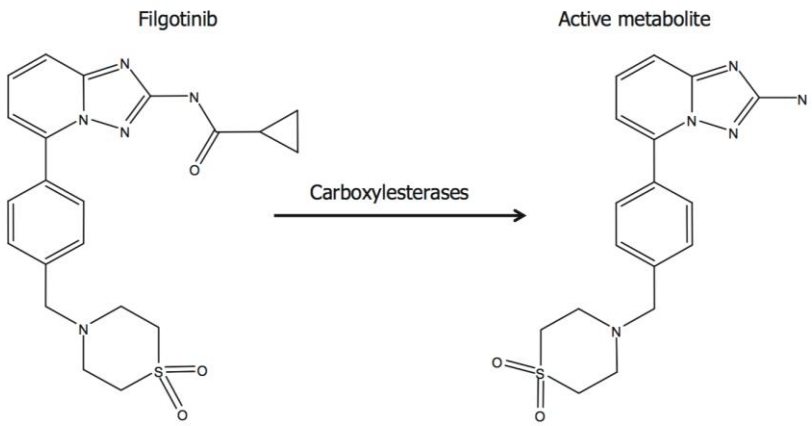
Genovese MC, et al. Ann Rheum Dis, 2016

Filgotinib

- Early clinical studies in healthy volunteers with the first selective Janus kinase 1 inhibitor, filgotinib, showed high exposure to an active metabolite that contributes to its overall pharmacodynamic effect

- Dose-dependent pharmacodynamic activity of combined filgotinib and its metabolite was shown in whole blood from healthy volunteers following oral dosing of filgotinib

- Pharmacokinetic/pharmacodynamic modeling and simulation show a maximal pharmacodynamic effect is achieved at daily dosing of 200 mg filgotinib, and this dose was selected as the highest in a phase IIB program in patients with rheumatoid arthritis



Namour F, et al. Clin Pharmacokinet. 2015

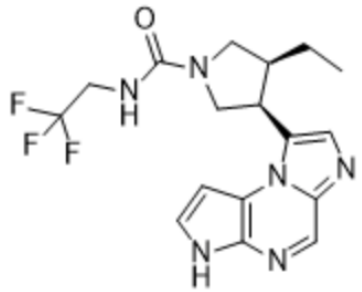
ABT-494 (Upadacitinib)

- ABT-494, a selective Janus kinase 1 inhibitor, was safe and well-tolerated at single oral doses up to 48 mg in healthy volunteers and at twice-daily doses up to 24 mg in healthy volunteers and rheumatoid arthritis (RA) patients using the immediate-release formulation

- ABT-494 pharmacokinetics is characterized by a short functional half-life, dose-proportional exposures, and lack of significant accumulation with twice-daily dosing; no pharmacokinetic interaction between methotrexate and ABT-494 was observed in subjects with RA

- The results supported advancing ABT-494 to phase II dose-ranging studies in RA and Crohn's disease

CHEMICAL STRUCTURE



Mohamed MF, et al. Clin Pharmacokinet. 2015

NIP-565

- NIP-565 inhibited JAK1 in the nM range, and showed more than 10-fold selectivity towards JAK2, JAK3, and Tyk2
- NIP-565 inhibited IL-6-induced phosphorylation of STAT1
- In a rat CIA model, NIP-565 attenuated paw swelling in a dose-dependent manner after repeated oral administration once per day for 15 days
- The risk of adverse events caused by NK cell attenuation with NIP-565 treatment may be lower than that with tofacitinib treatment
- Additionally, NIP-565 showed weaker inhibitory effect than other JAK inhibitors (e.g., tofacitinib, baricitinib and peficitinib) in human erythropoiesis assay, NIP-565 could be enough exposure to provide high therapeutic efficacy without anemia in clinical practice by once daily oral administration

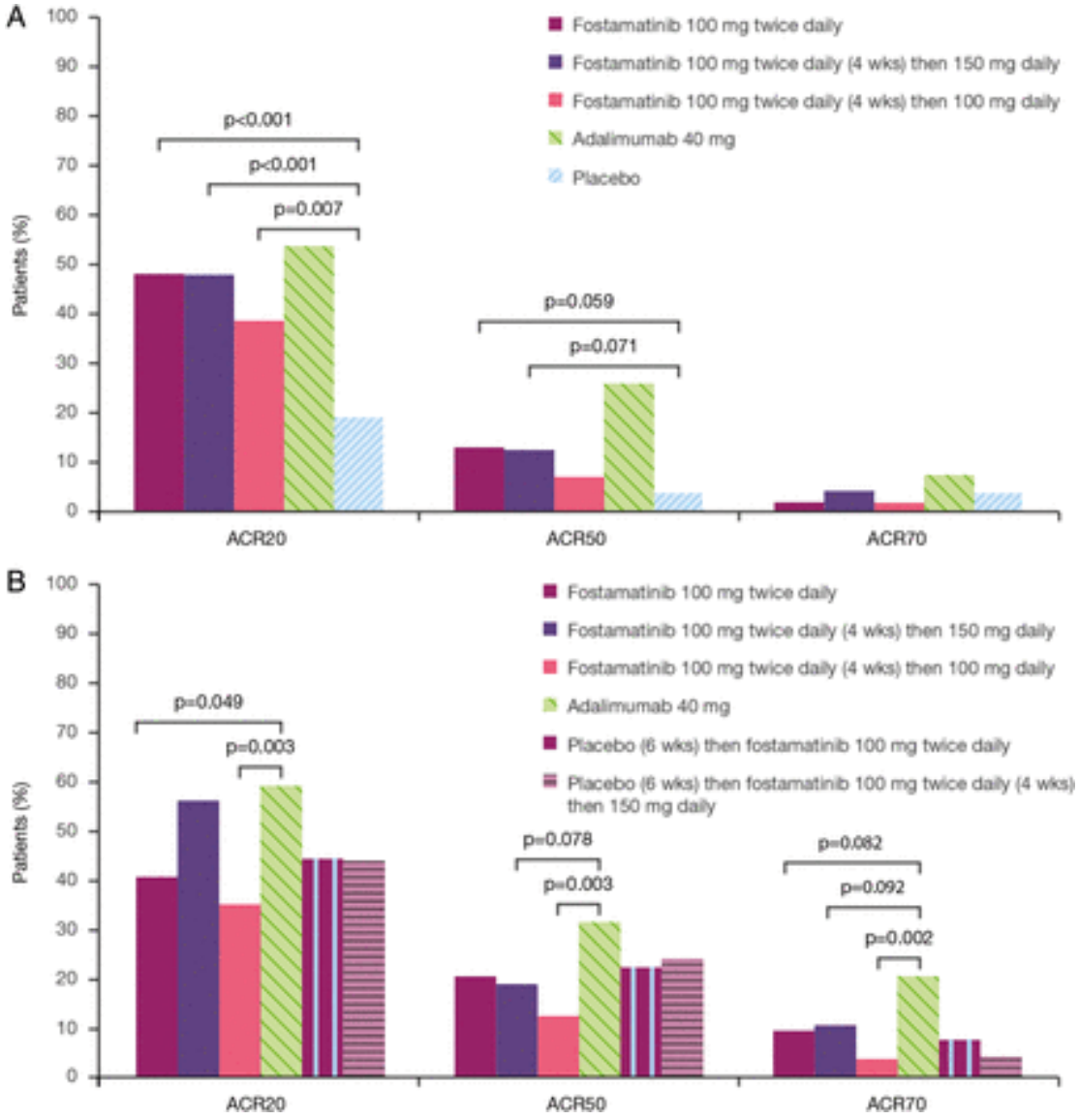
Hidaka Y et al. ACR 2015 (abstract)

Targeting small molecules

- Inhibitors of the JAK-STAT signaling pathway
- **Syk kinase inhibitors**
- **Phosphodiesterase-4 inhibitors**
- **MAPK p38 inhibitors**

Fostamatinib

Fostamatinib demonstrated efficacy as monotherapy, showing superior DAS-28(CRP) score changes between baseline and 6 weeks when compared with placebo in treatment arms A and B. However, all fostamatinib regimens demonstrated inferior responses compared with adalimumab at Week 24



Taylor PC et al, Arthritis Rheumatol 2014

Apremilast

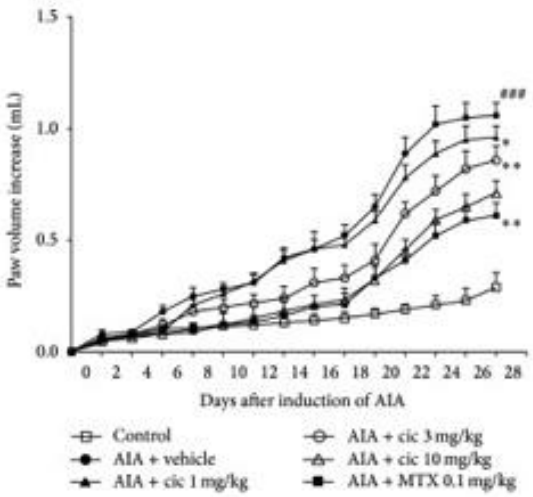
Apremilast efficacy was not demonstrated in patients who had active RA despite stable MTX therapy

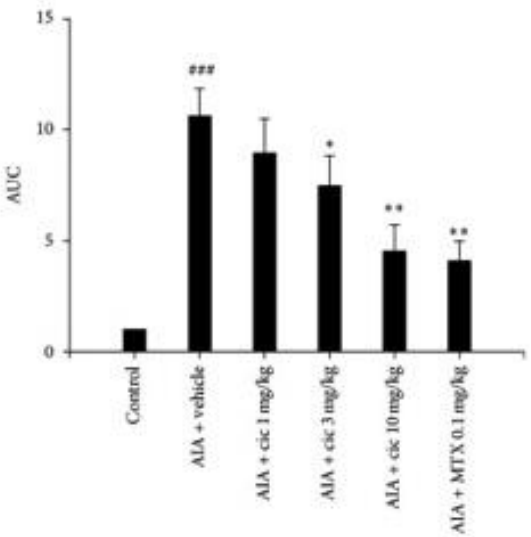
Table 2. Secondary end points at week 24*

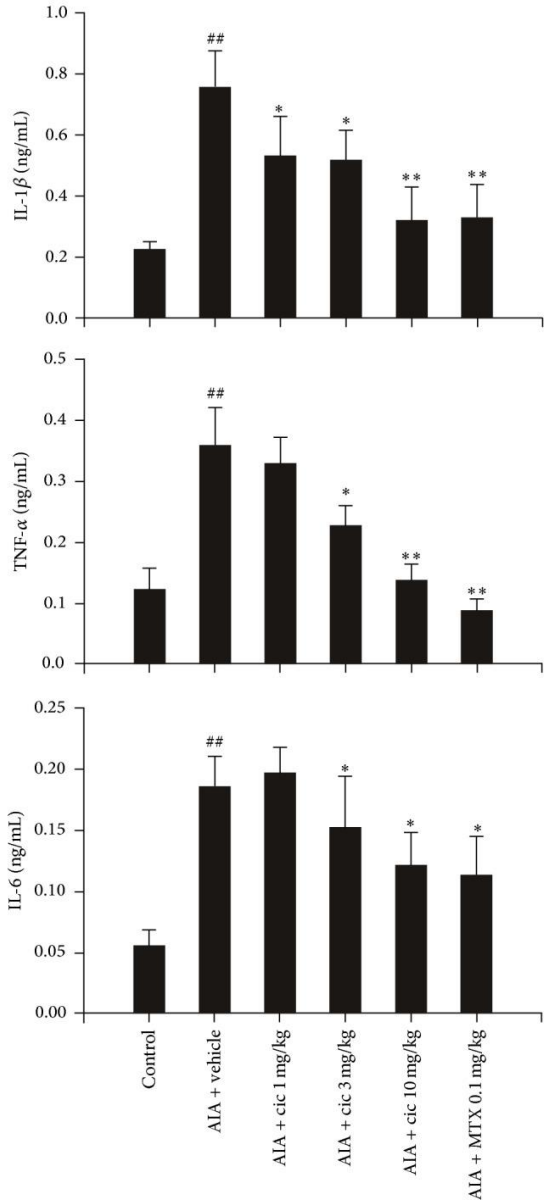
	Apremilast		
	Placebo (n = 79)	20 mg twice a day (n = 82)	30 mg twice a day (n = 76)
ACR20, %	24.1	19.5	27.6
ACR50, %	6.3	4.9	15.8
ACR70, %	3.8	2.4	5.3
SJC (range 0–66), mean ± SD change†	−5 ± 8	−5 ± 8	−6 ± 9
TJC (range 0–68), mean ± SD change†	−7 ± 11	−6 ± 10	−7 ± 13
HAQ DI (range 0–3), mean ± SD change‡	−0.07 ± 0.43	−0.08 ± 0.47	−0.23 ± 0.5
CDAI (range 0–76), mean ± SD change§	−10.9 ± 15.1	−9.2 ± 13.1	−11.4 ± 14.6
DAS28-CRP <2.6, %	7.6	7.3	6.6
EULAR (CRP) good/moderate response, %	40.5	29.3	35.5

Genovese MC et al, Arthritis Rheumatol 2015

Ciclamilast







Ciclamilast, a novel and selective PDE4 inhibitor, in daily oral administration at 1, 3, and 10 mg/kg dose-dependently inhibited the increase in hind paw volume of rats with AIA.

The inhibition of paw edema was associated with inhibition of both the production of cytokines such as TNF-α, IL-1β, and IL-6 and cell infiltration assessed in subcutaneous paw tissue.

Moreover, there was significantly less tissue destruction in the ciclamilast-treated rats compared to the vehicle-treated rats, as assessed by radiographic analysis and histopathological evaluation..

Zhang ZC et al, Biomed Res Int. 2015

Outline

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Biosimilars

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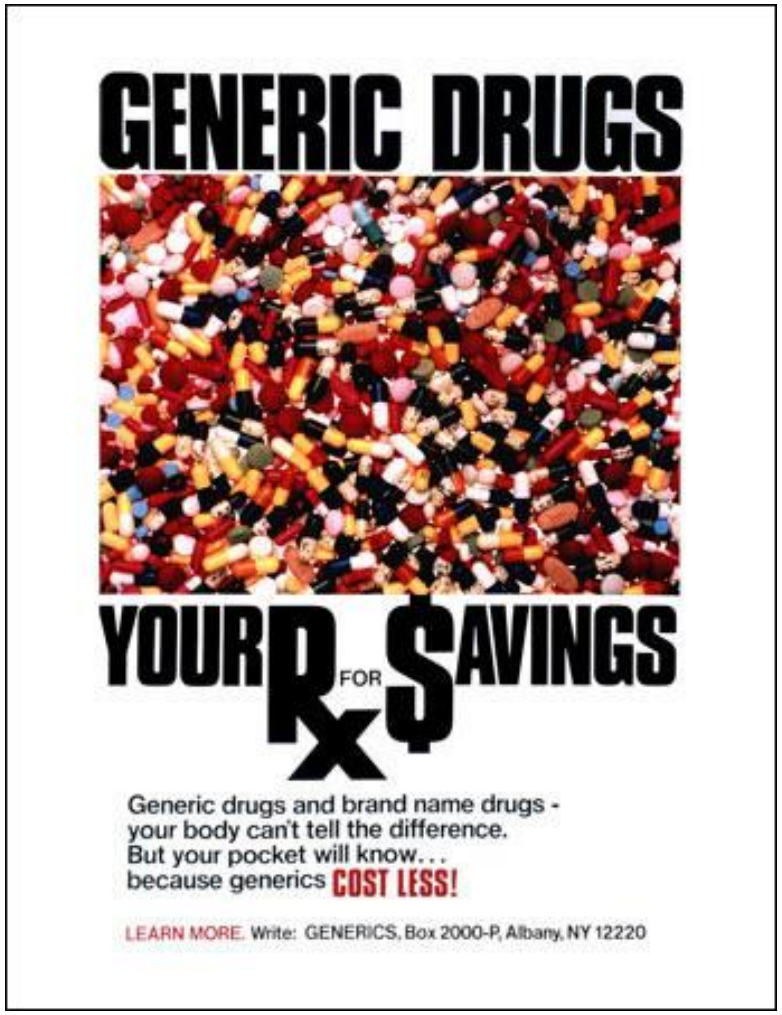
Today

Biosimilars in rheumatology: ready for prime time?

Definition (EMA 2008):
a medicine which is similar
to a biological medicine
that has already been authorised
(the ‘biological reference medicine’)

A generic medicine contains the same active medicinal substance as an originator pharmaceutical product. Because it acts in the same way in the human body it is interchangeable with the originator product.

Biosimilars cannot be “biogeneric”



Biosimilars

	Originator	Status
CT-P13	Remicade	EMA approved for rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn's disease and ulcerative colitis
SB4	Enbrel	EMA recommended marketing authorization for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, severe non-radiographic axial spondyloarthritis, plaque psoriasis

Table 1 Biosimilars for rheumatic diseases for which data have been published in peer-reviewed journals or presented at international scientific meetings

Reference product	Biosimilar molecules
Adalimumab	ABP501
	BI 695501
	CHS-1420
	GP-2017
	M923
	SB5
	ZRC-3197
Etanercept	CHS-0214
	GP2015
	HD203
	SB4*
Infliximab	BOW015†
	CT-P13*‡
	PF-06438179
	SB2
Rituximab	CT-P10
	GP2013
	PF-05280586

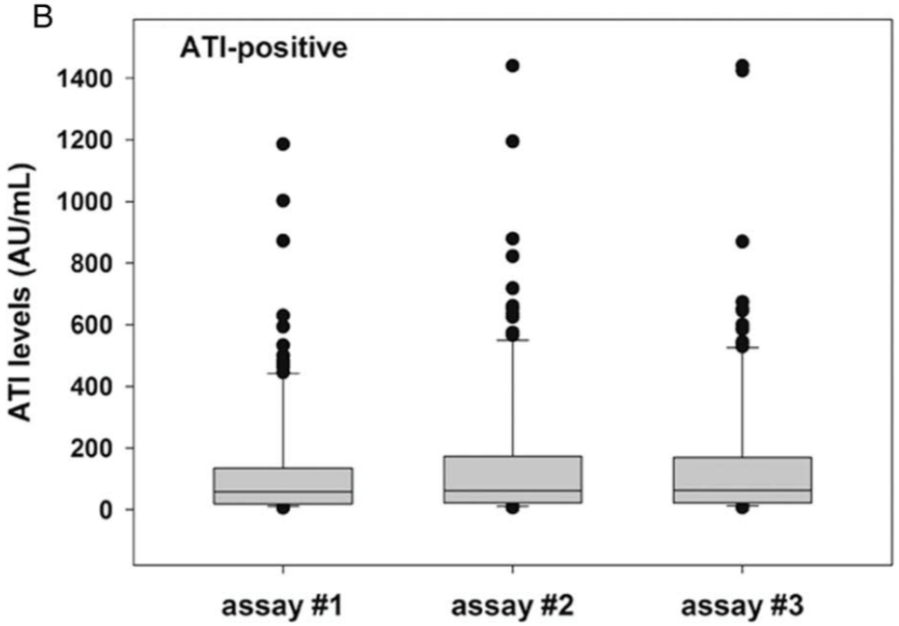
Dörner T et al, Ann Rheum Dis 2016

Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study

A phase III randomized study to evaluate the efficacy and safety of CT-P13 compared with reference infliximab in patients with active rheumatoid arthritis: 54-week results from the PLANETRA study

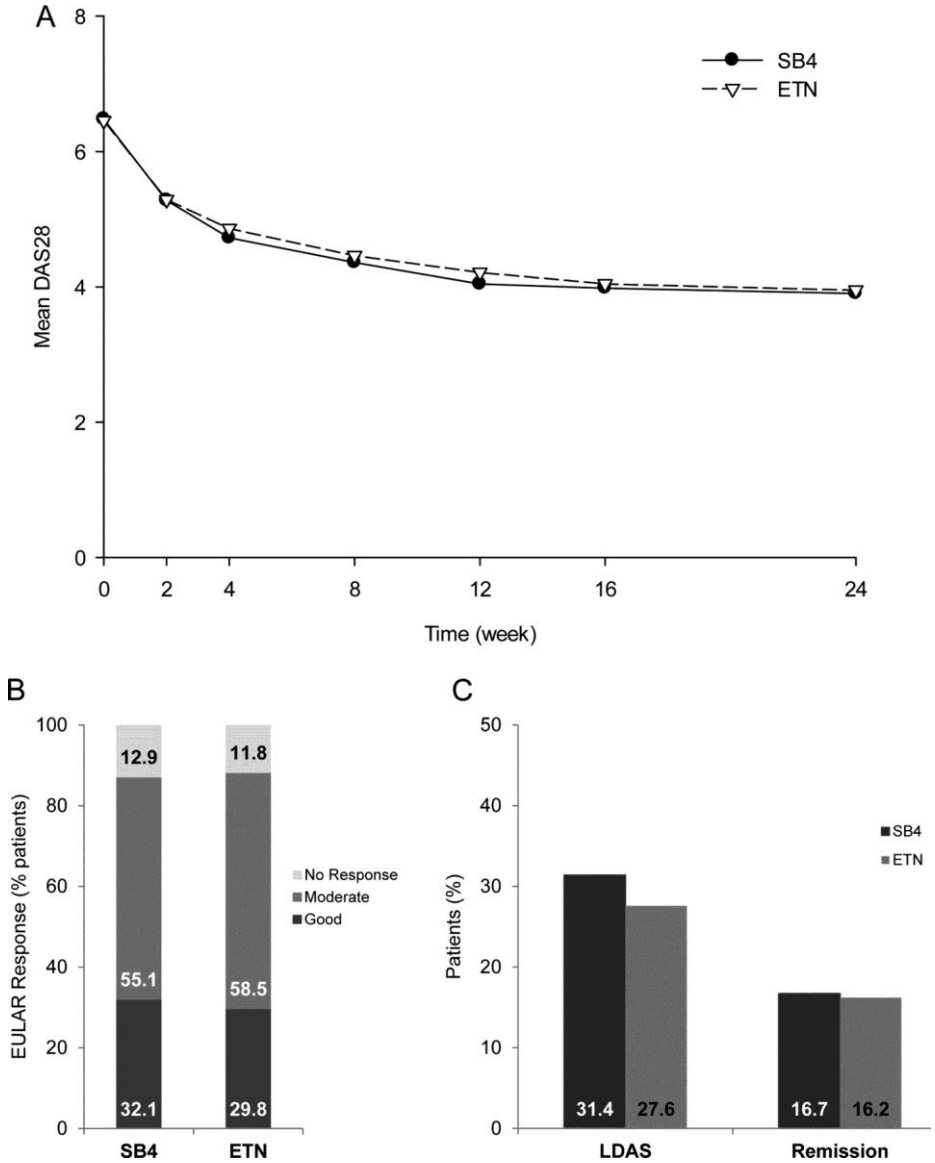
Antibodies to infliximab in Remicade-treated rheumatic patients show identical reactivity towards biosimilars

All patients tested ATI-positive in assay #1 (n=126) were found positive when either Remsima or Inflectra was used to detect the antibodies



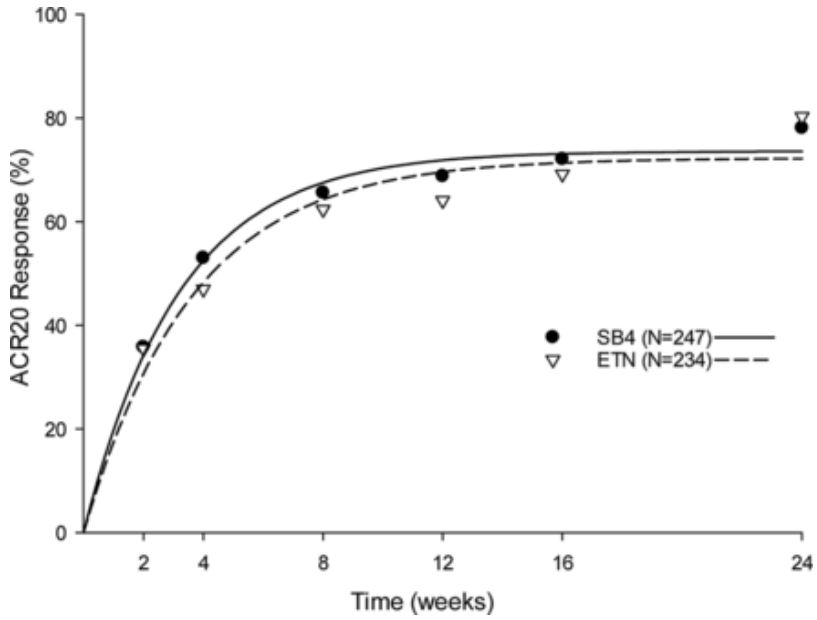
Ruiz-Argüello MB et al, Ann Rheum Dis 2016

Etanercept biosimilar
SP4



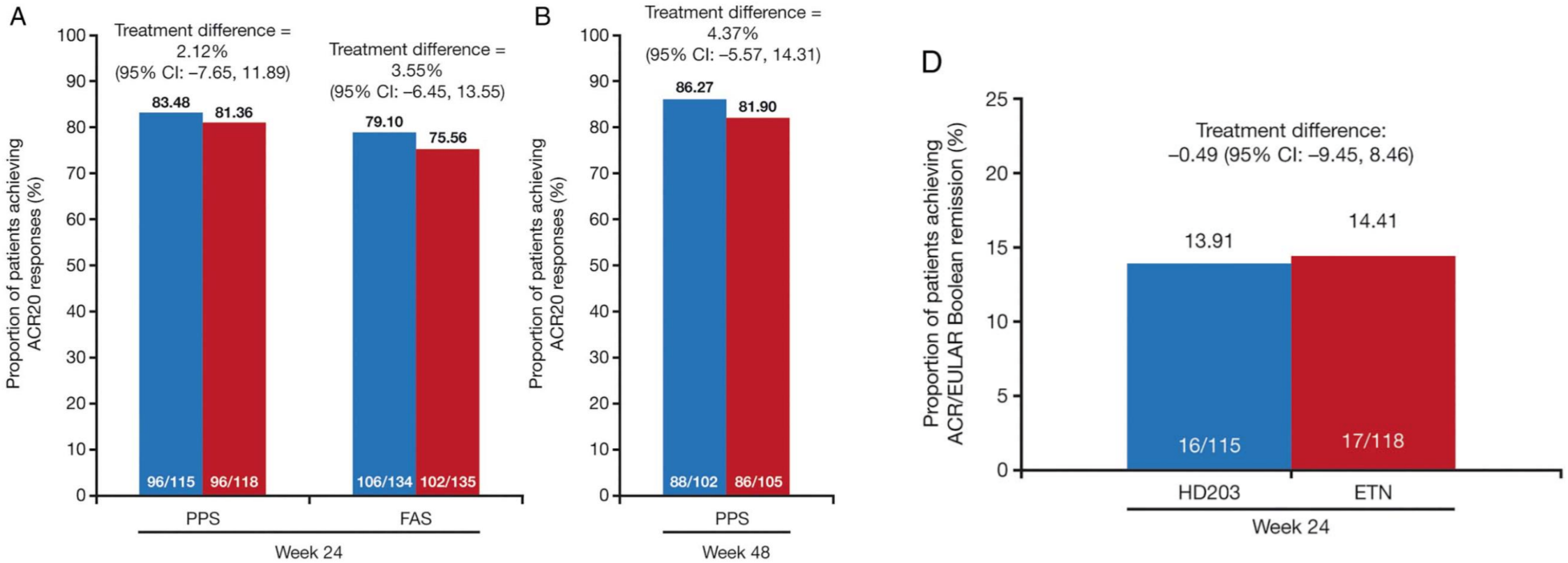
SB4 was shown to be equivalent with ETN in terms of efficacy at week 24. SB4 was well tolerated with a lower immunogenicity profile

The safety profile of SB4 was comparable with that of ETN



Emery P et al. Ann Rheum Dis 2015

Etanercept biosimilar
HD203
HERA study



Bae SC et al. Ann Rheum Dis 2015

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B cell targeting

Compound	Company	Structure	Devt stage	Target
Ocrelizumab	Roche	Monoclonal	Terminated	CD20
Ofatumumab	GSK-Genmab	Monoclonal	Phase III	CD20
Belimumab	GSK	Monoclonal	Phase II	BLyS
Atacicept	EMD-Serono	Fusion protein	Phase II	APRIL/BLyS
Tabalumab (LY2127399)	Eli Lilly	Monoclonal	Terminated	BLyS

Selmi C et al, Immunol Res 2014

Ofatumumab - humanized anti-CD20 monoclonal antibody

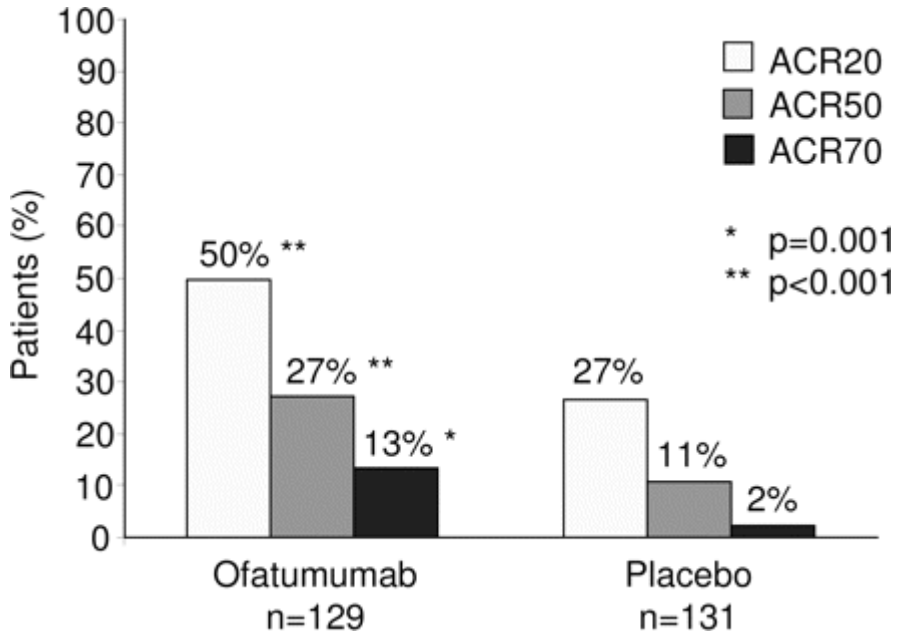
- It recognizes a unique membrane proximal epitope that differs from the epitope recognized by rituximab and ocrelizumab, and may account for a higher efficiency of B-cell killing in vitro and in vivo.

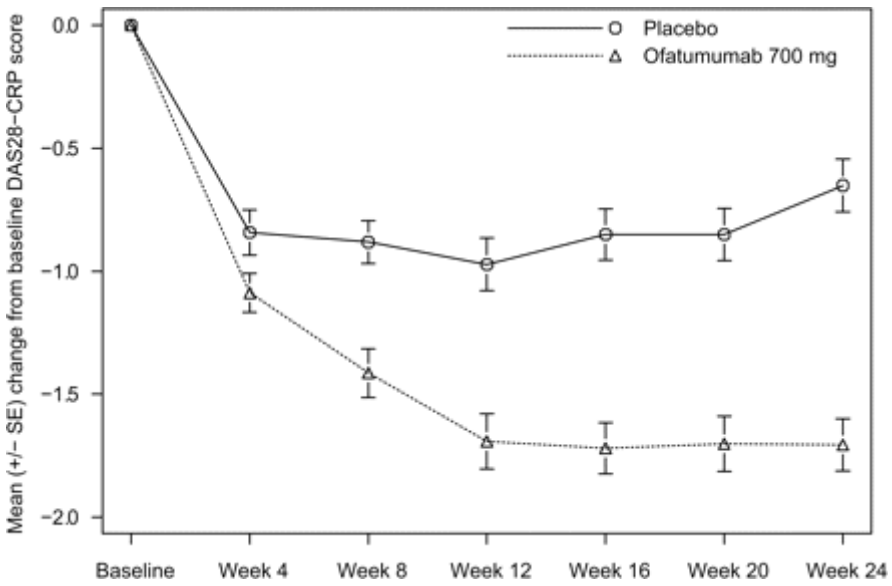
- Ofatumumab significantly improved all clinical outcomes in biological-naıve RA patients. There was no detected immunogenicity at week 24.

- The Phase III trial investigating the efficacy of ofatumumab in active, TNF antagonist (one or more) inadequate responder, RA patients is ongoing

Selmi C et al, Immunol Res 2014

Ofatumumab - humanized anti-CD20 monoclonal antibody





Taylor PC et al, Immunol Res 2011

Chemokine targeting

Compound	Company	Structure	Devt stage	Target
MLN1202	Millenniun	Monoclonal	Terminated	CCR2
ABN912	Novartis	Monoclonal	Terminated	CCL2
Maraviroc	ViiV	Small molecule	Terminated	CCR5
SCH351125	Schering-Plough	Small molecule	Terminated	CCR5
AZD5672	AstraZeneca	Small molecule	Terminated	CCR5
CCX354-C	ChemoCentryx	Small molecule	Phase II	CCR1
CP-481,715	Pfizer	Monoclonal	Phase I	CCR1
MLN3897	Millennium	Small molecule	Terminated	CCR1
MDX-1100	Medarex/BMS	Monoclonal	Phase II	CXCL-10

Selmi C et al, Immunol Res 2014

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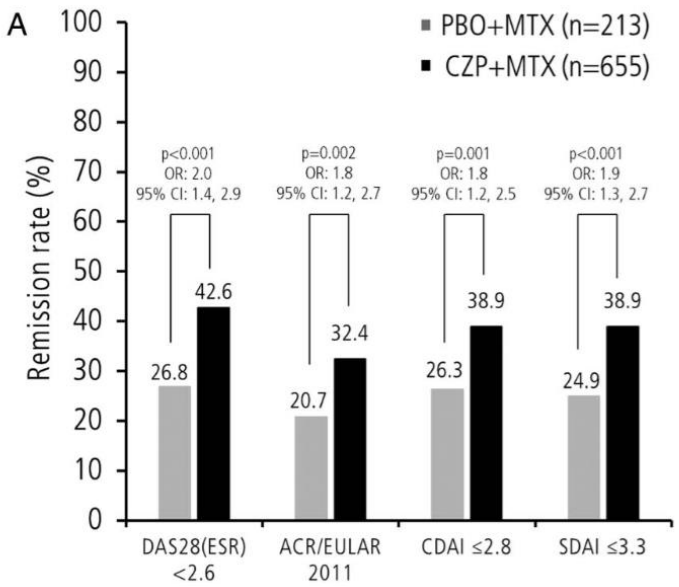
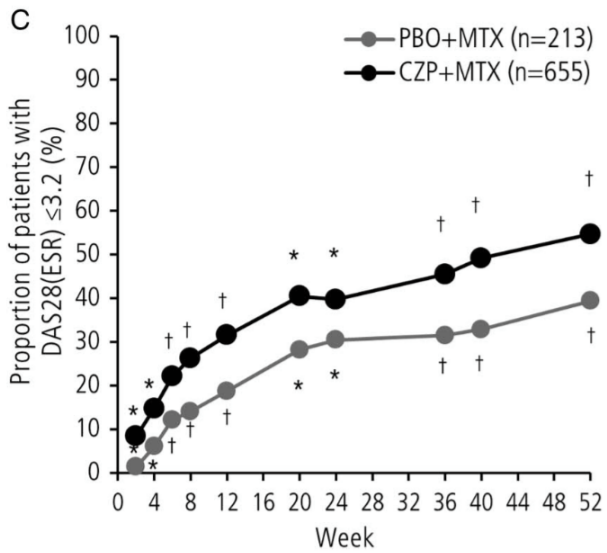
DMARD combination therapy

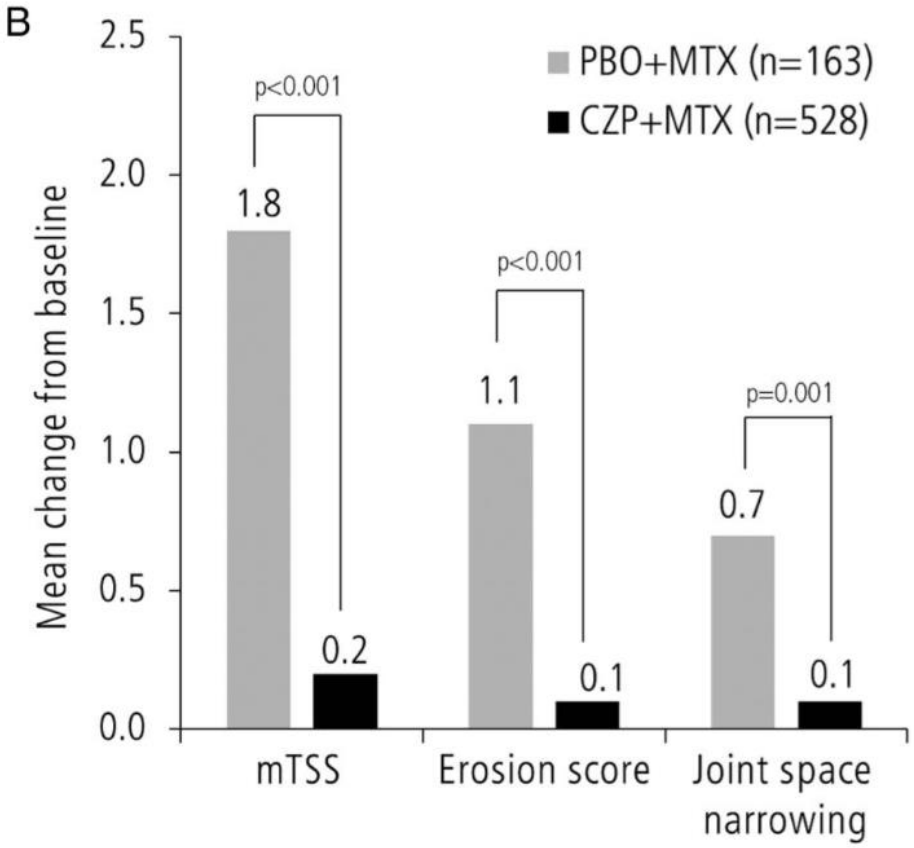
- New triple therapy: methotrexate, salazosulfapyridine and bucillamine
- DAS28 scores: DMARDs combination group: 4.84 ± 0.96; TNF-inhibiting biologics group: 5.23 ± 1.26, no significant difference between the two groups
- No difference between the two groups at 12 months (DAS28, 3.39 ± 1.43 and 3.05 ± 1.43, $p = 0.39$)
- No significant difference in the degree of bone destruction between the two groups at 12 months
- The triple DMARD combination therapy provided a new treatment option for those patients for whom treatment with biologics is difficult

Matsuno T et al, Mod Rheumatol 2016

Certolizumab in DMARDs naïve RA

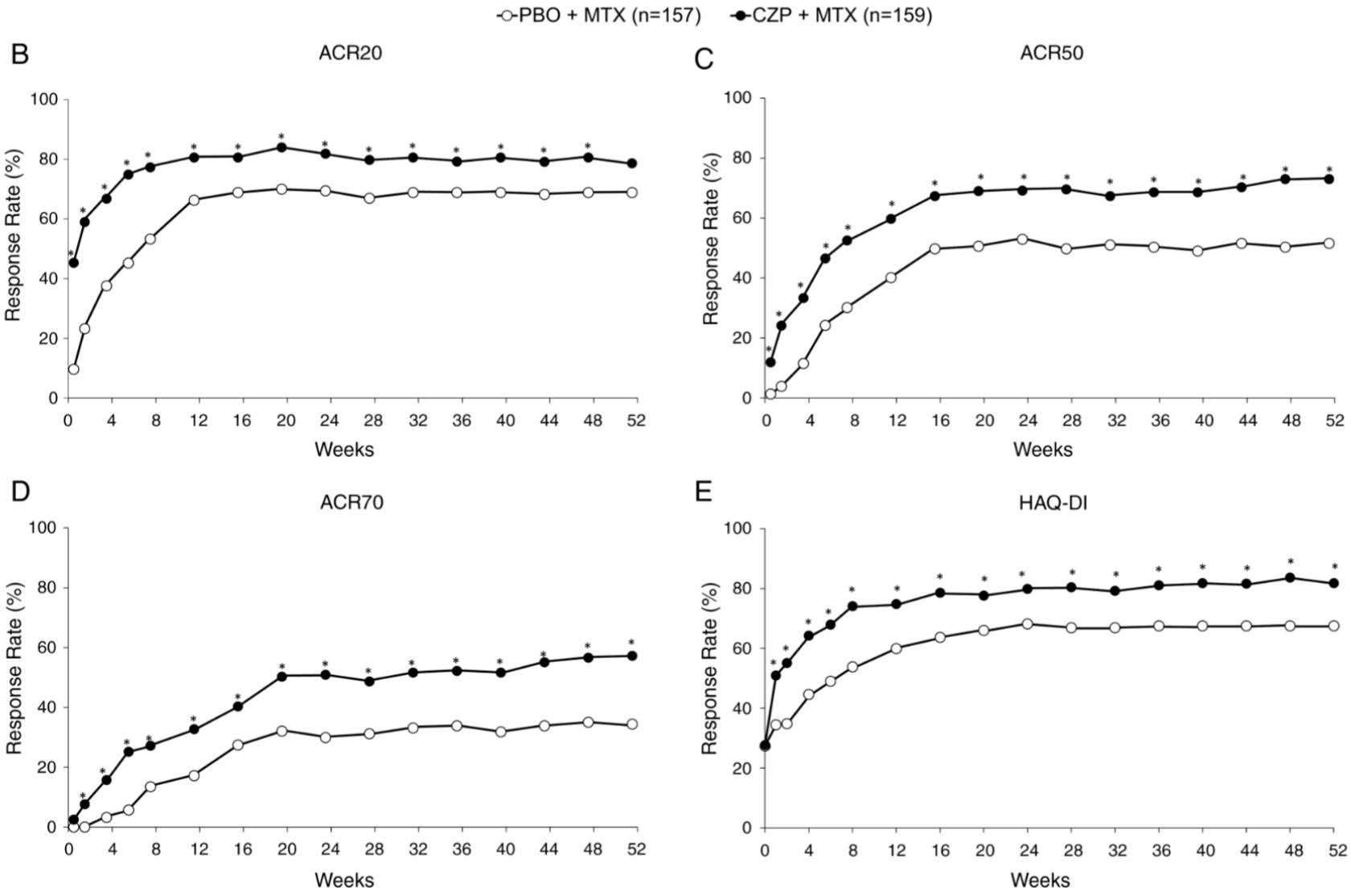






Emery P at al., Ann Rheum Dis, 2016

Certolizumab in DMARDs naïve RA
C-OPERA



Atsumi T at al., Ann Rheum Dis, 2016

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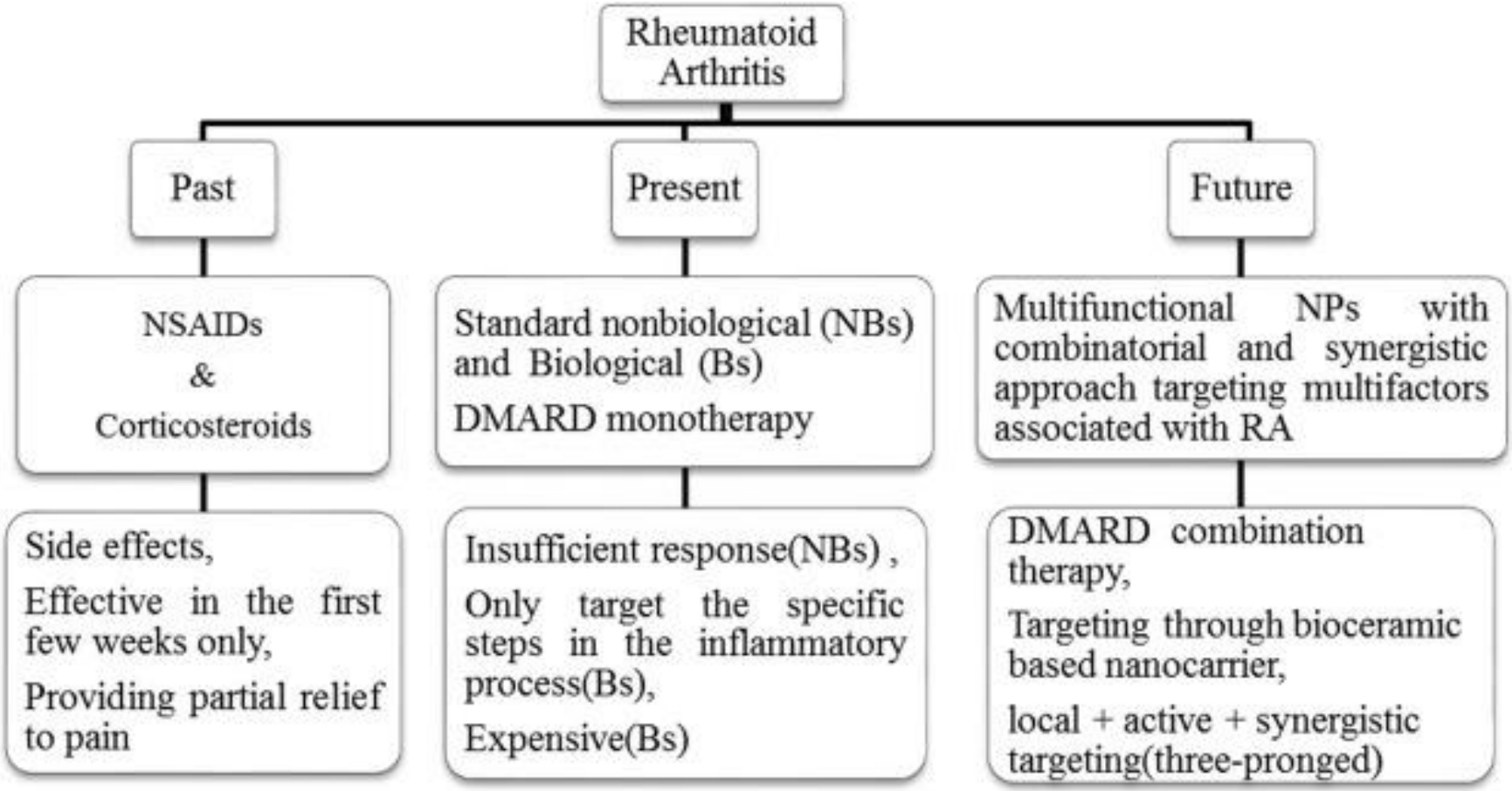
Tomorrow
Nanoparticles

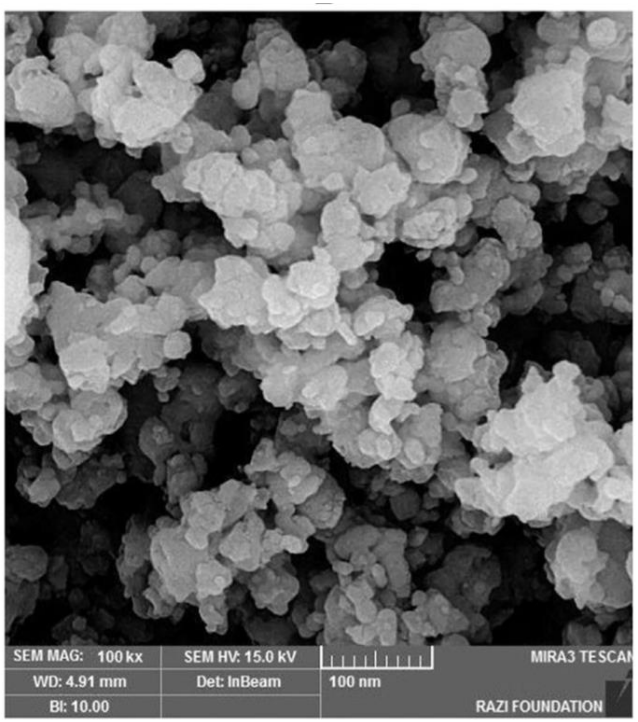


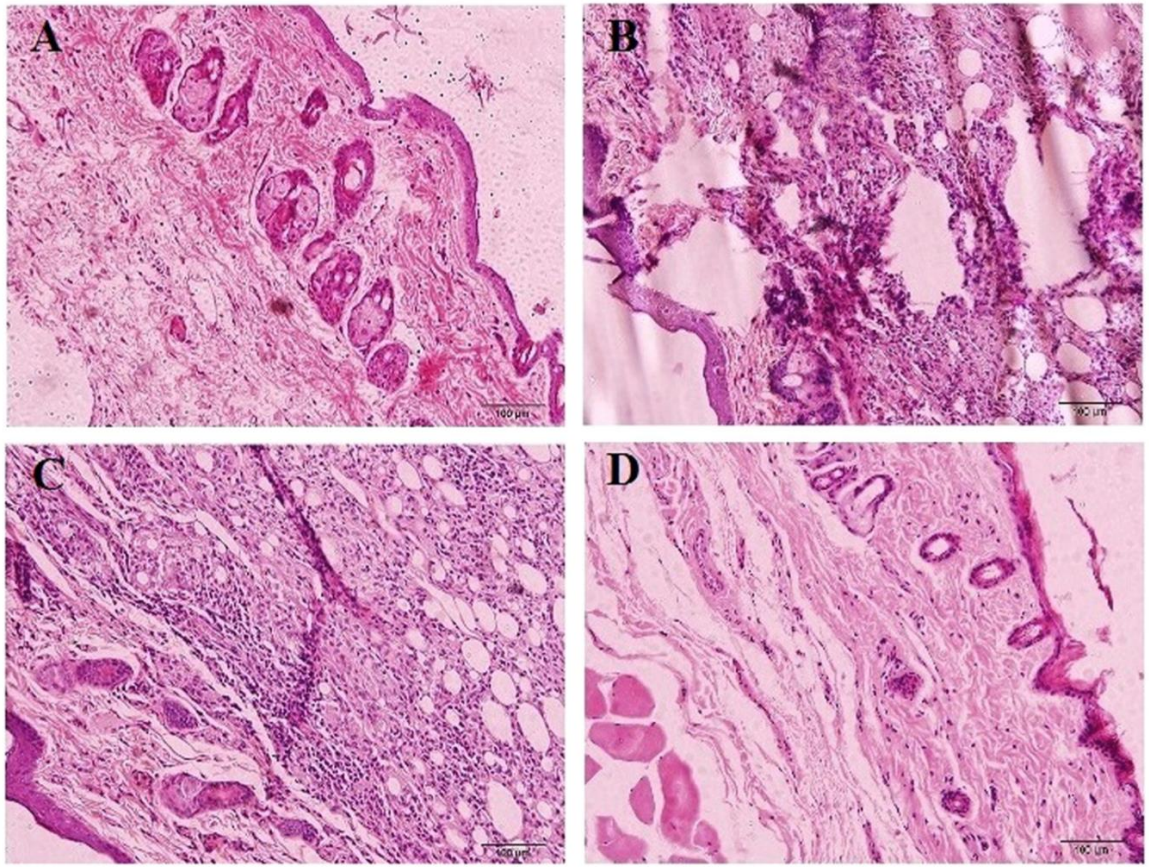
Pandey S, Med Hypothesis 2016

Tomorrow

Nanoparticles

Methylprednisolone acetate-loaded hydroxyapatite nanoparticles as a potential drug delivery system for treatment of rheumatoid arthritis: *In vitro* and *in vivo* evaluations





Jafari S et al, Eur J Pharm Sci 2016

Tomorrow

Nanoparticles

Fabrication and efficacy evaluation of chloroquine nanoparticles in CFA-induced arthritic rats using TNF-α ELISA

Pharmaceutical potential of tacrolimus-loaded albumin nanoparticles having targetability to rheumatoid arthritis tissues

Curcumin loaded solid lipid nanoparticles ameliorate adjuvant-induced arthritis in rats

Bhalekar MR et al, Eur J Pharm Sci 2016
Thao le Q et al, Int J Pharm. 2016
Arora R et al, Eur J Pain. 2015

RHEUMATOID ARTHRITIS

Targeting phosphatase-dependent proteoglycan switch for rheumatoid arthritis therapy

- Fibroblast-like synoviocytes are activated during RA and mediate joint inflammation and destruction of cartilage and bone.
- RPTPσ, a transmembrane tyrosine phosphatase, as a therapeutic target for FLS-directed therapy
- RPTPσ is reciprocally regulated by interactions with chondroitin sulfate or heparan sulfate containing extracellular proteoglycans in a mechanism called the proteoglycan switch
- The proteoglycan switch regulates FLS function:
  - Incubation of FLS with a proteoglycan-binding RPTPσ decoy protein inhibited cell invasiveness and attachment to cartilage by disrupting a constitutive interaction between RPTPσ and the heparan sulfate proteoglycan syndecan-4.
  - RPTPσ mediated the effect of proteoglycans on FLS signaling by regulating the phosphorylation and cytoskeletal localization of ezrin
  - Administration of the RPTPσ decoy protein ameliorated in vivo human FLS invasiveness and arthritis severity in the K/BxN serum transfer model of RA

Doody KM et al, Science Translational Research 2015

Evasins: Therapeutic Potential of a New Family of Chemokine-Binding Proteins from Ticks

Evasins are chemokine-binding proteins (CKBPs)

- Evasin-1: highly specific for CCL3, CCL4 and CCL18
- Evasin-3: subset of CXC chemokines, ELR+ family, i.e. CXCL1,-2,-3,-5,-6, and -8
- Evasin-4: interacts with at least 18 CK, only members of the CC subfamily
- Evasin 1 and 3 inhibit neutrophil migration in mice

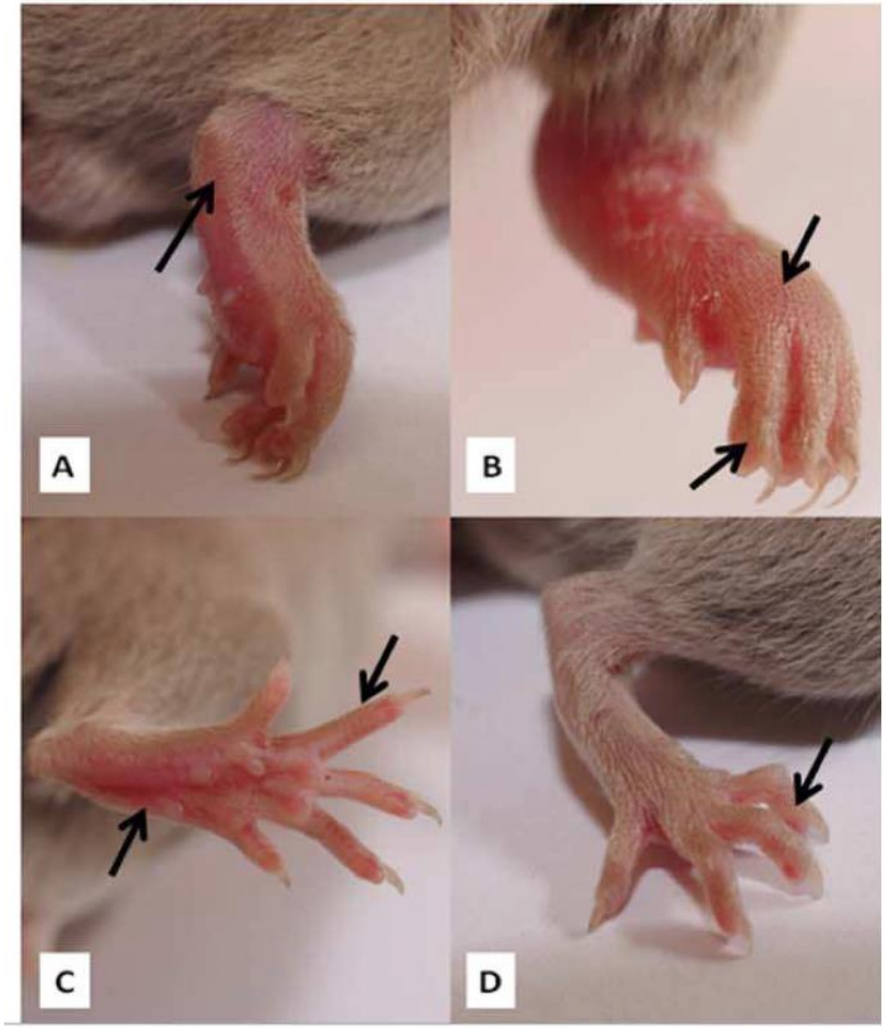
In arthritis animal model, the administration of Evasin-3 reduce disease symptoms

Bonvin P et al, Front Immunol 2016

Clinical and Experimental Immunology ORIGINAL ARTICLE doi:10.1111/cei.12745

Novel therapeutic compound tuftsin–phosphorylcholine attenuates collagen-induced arthritis

Treatment with helminthes and helminthes ova improved the clinical symptoms of several autoimmune diseases in patients and in animal models. Phosphorylcholine (PC) proved to be the immunomodulatory molecule.



Bashi T et al, Clin Exp Immunol 2015

Conclusions

- New cytokines inhibitors are approaching the market, especially anti-IL6;
- Biosimilars are already on the market
- Small molecules will represent the next future
- Old drugs might be used with different treatment schemes and maybe changing the treatment paradigms
- New delivery methods or molecular targets (chemokines) will be the future?

Thanks for your attention!

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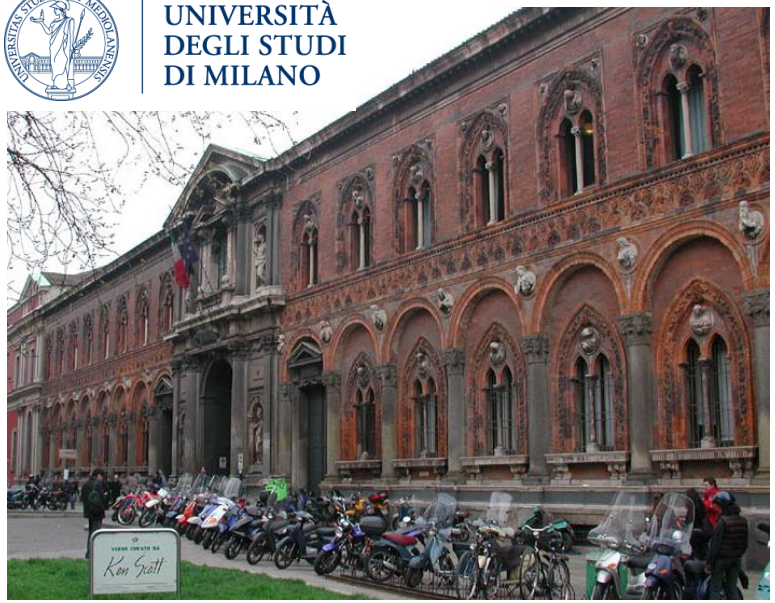
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