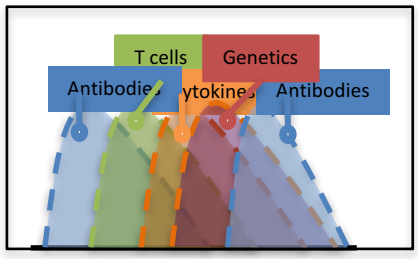
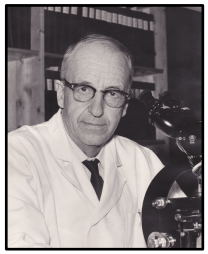
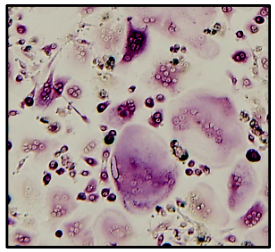
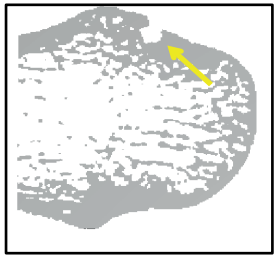
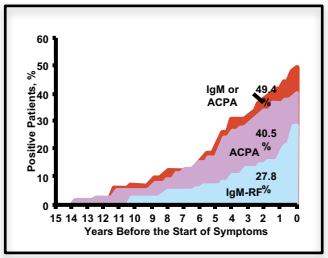
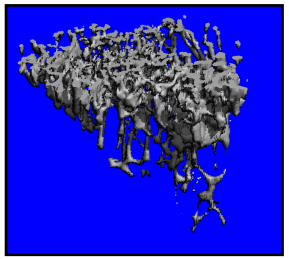
GENOVA 2016

ACPA/RF and the Bone

Georg Schett
Department of Medicine 3
University of Erlangen-Nuremberg
Erlangen, Germany



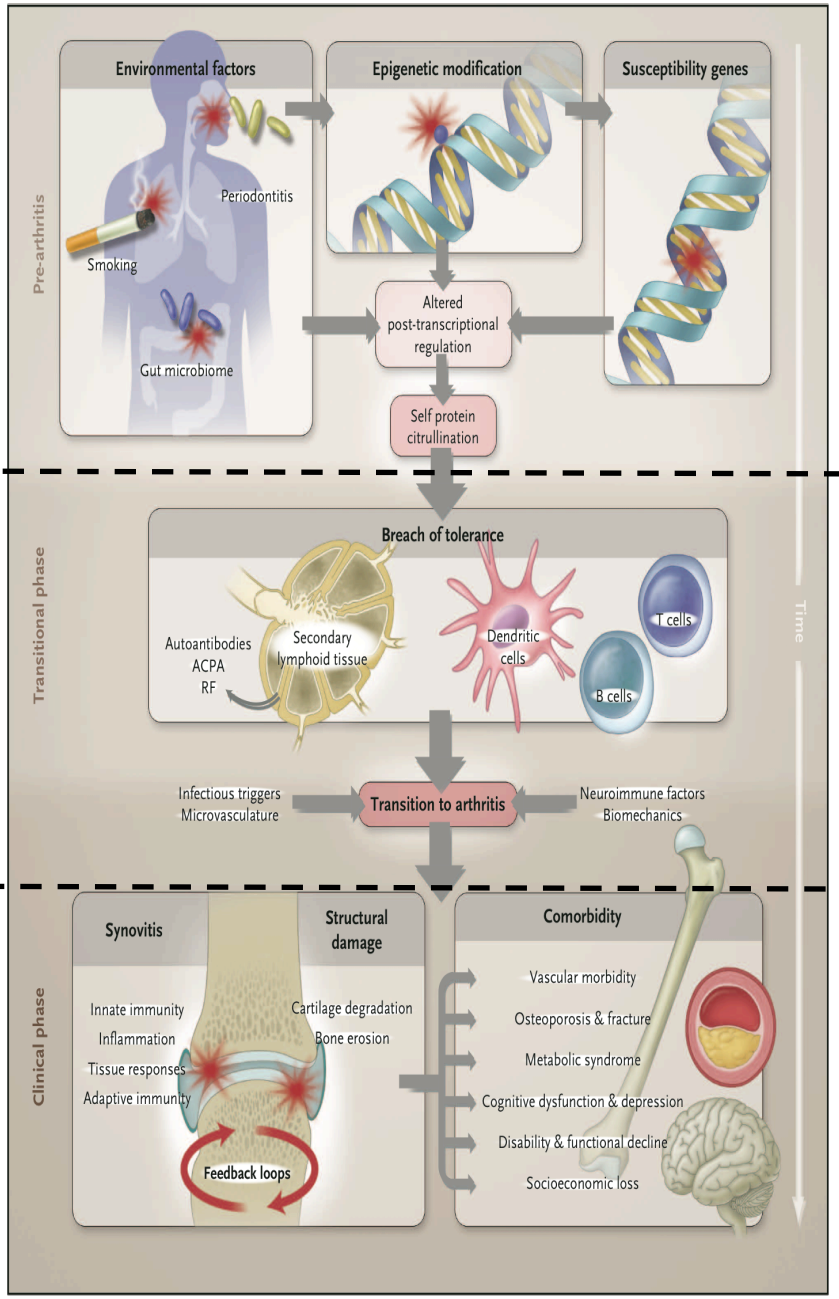







Rheumatoid Arthritis

AUTO IMMUNITY

INFLAMMATION



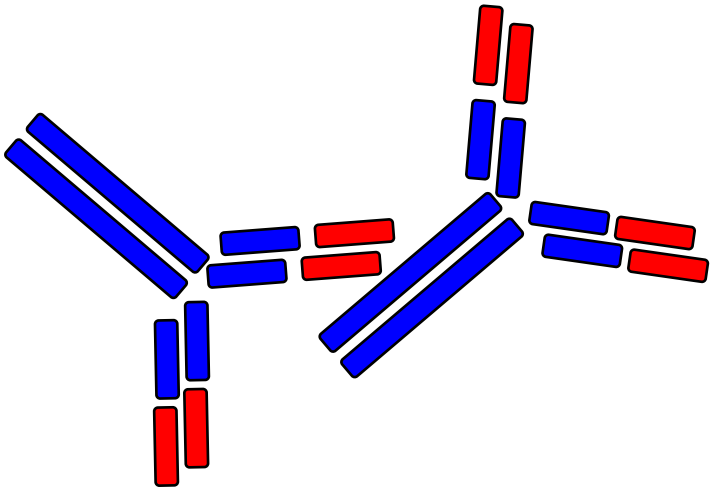
TOPICS

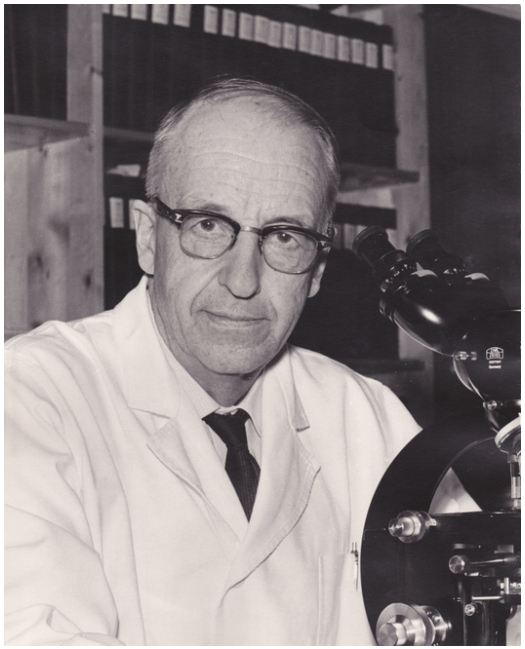
1. ACPA and AMPA
2. Pathophysiologic role of ACPA and RF on the bone
3. ACPA/AMPA and disease course of RA
4. DMARDs and ACPA

1940- Discovery of rheumatoid factor

*„On the occurence of a **factor in human serum** activating the specific agglutination of sheep red corpuscules“*

Eric Waaler. Acta Pathol Microbiol Scand 1940; 17:172-188.

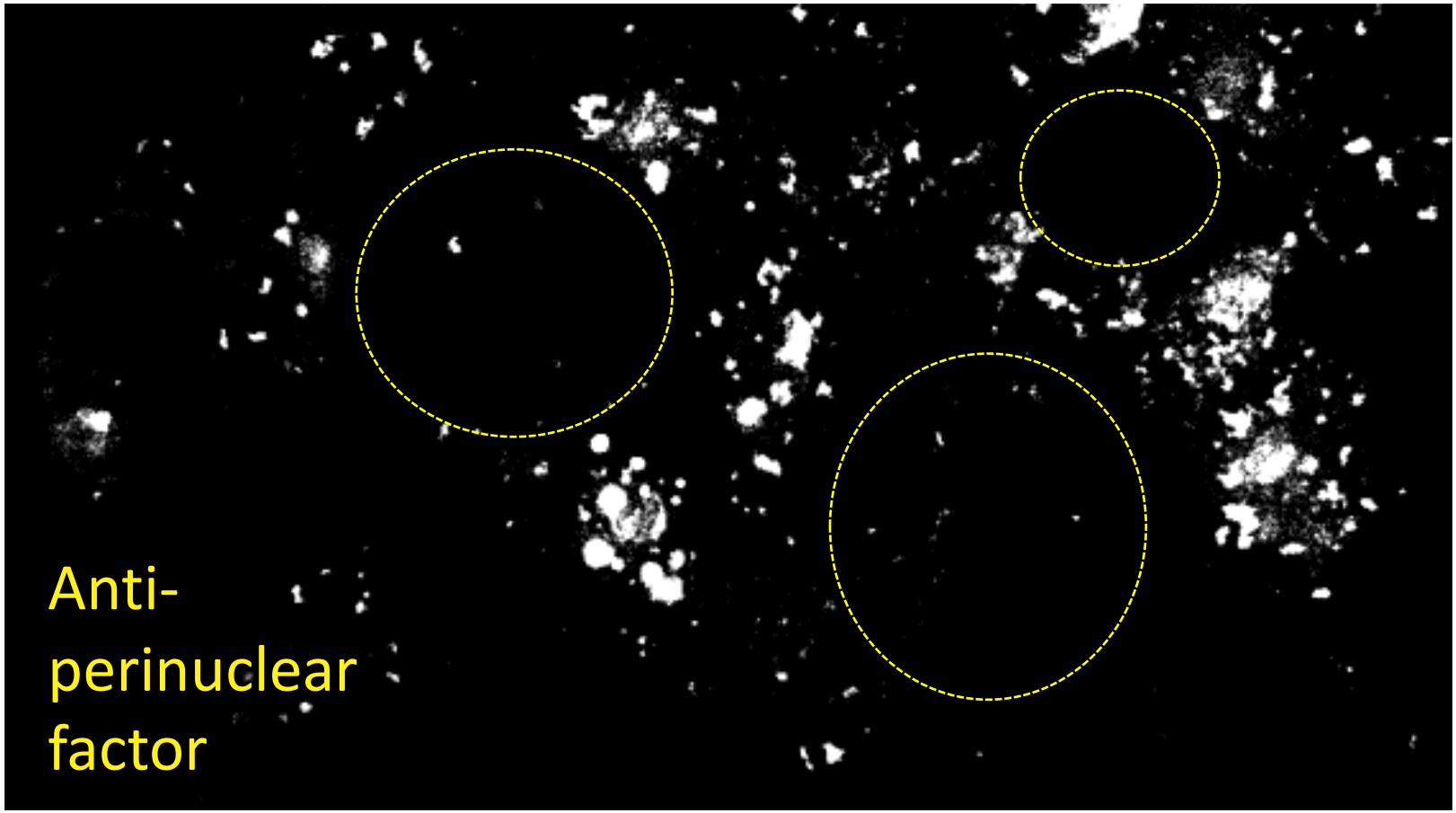




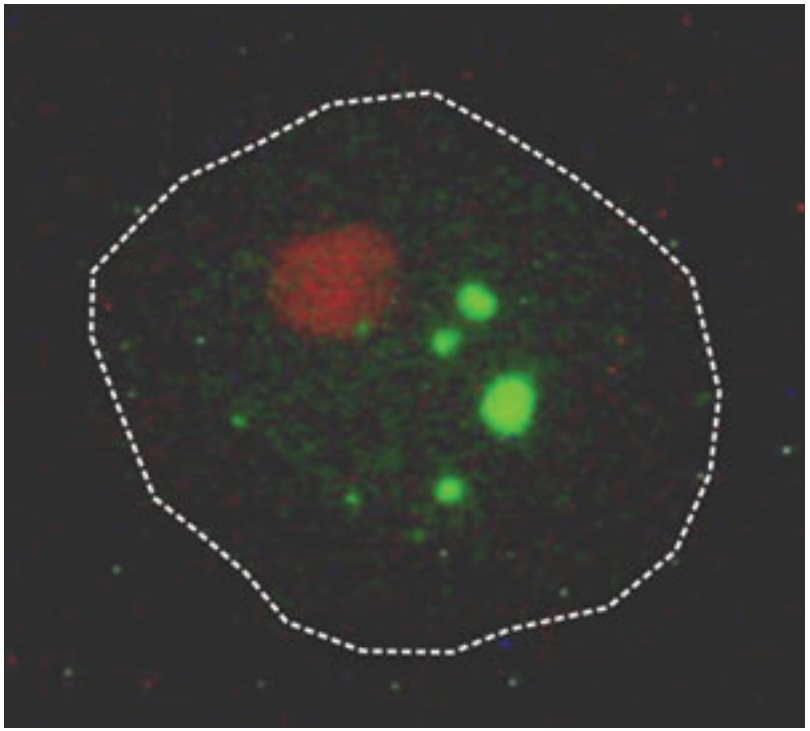
Eric Waaler
1903-1997

Anti-modifyfied protein antibody response: Discovered more than 50 years ago

Nienhuis RLF, et al. New Serum Factor in Patients with Rheumatoid Arthritis: The Antiperinuclear Factor. Ann Rheum Dis. 1964 Jul; 23(4): 302–305.



Anti-perinuclear factor (APF)



Staining of granules adjacent to the nucleaus in human buccal mucosa epithelium

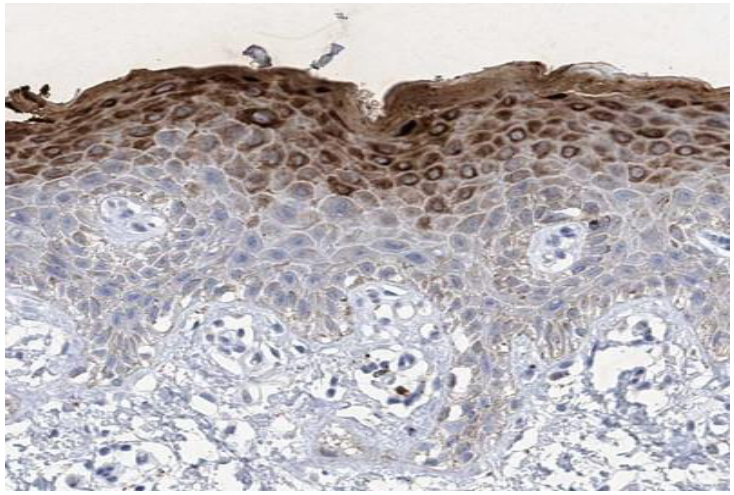
Nienhuis RLF, et al. Ann Rheum Dis. 1964 Jul; 23(4): 302–305.

Walther J. van Venrooij, et al.
*Nature Reviews Rheumatology **7**, 391-398*

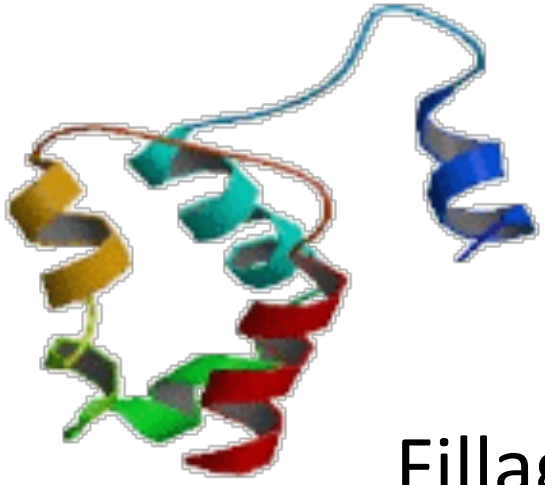
Diagnosis		Waaler-Rose and Latex Test		Waaler-Rose Test		APF-Positive
		Positive	Negative	Positive	Negative	
Rheumatoid Arthritis	Definite	48	9	4	4	65
	Probable and Possible	6	2	—	—	8
Systemic Lupus Erythematosus		1	—	—	—	1

„Anti- Keratin antibodies“

- Positive staining of the *Stratum corneum* of rat esophageal epithelium by serum from patients with RA.
  Young et al Br Med J 1979; 2: 97-99
- Anti-keratin antibodies was a misnomer because the antibodies were not directed against keratin but fillaggrin
- Antigen was identified as fillagrin
  Simon M et al, J Clin Invest 1993; 92: 1387-1393

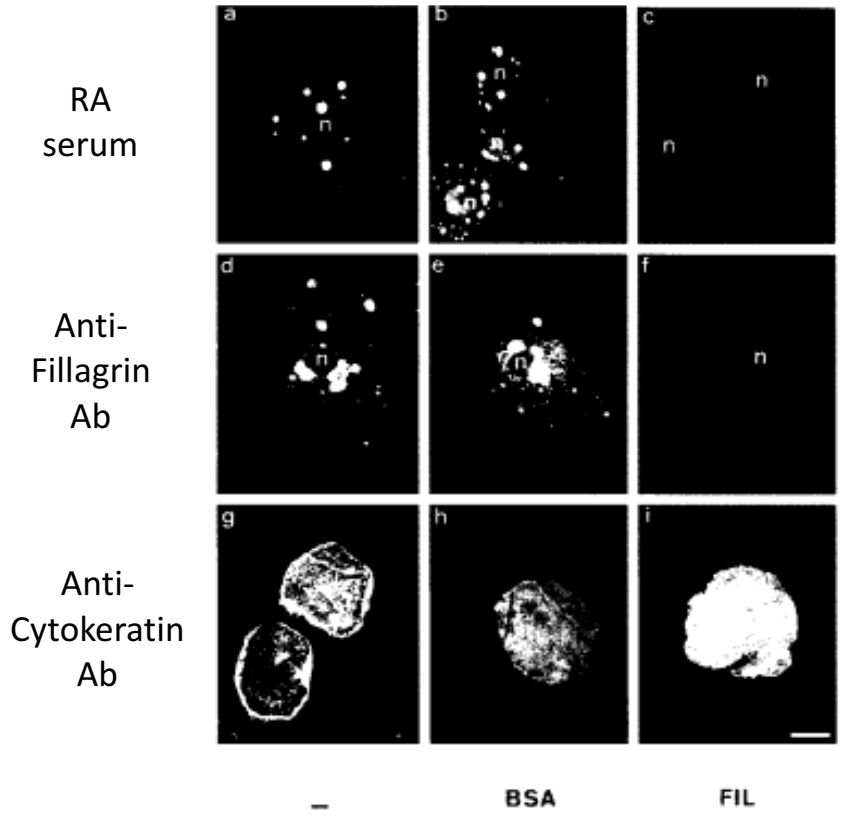


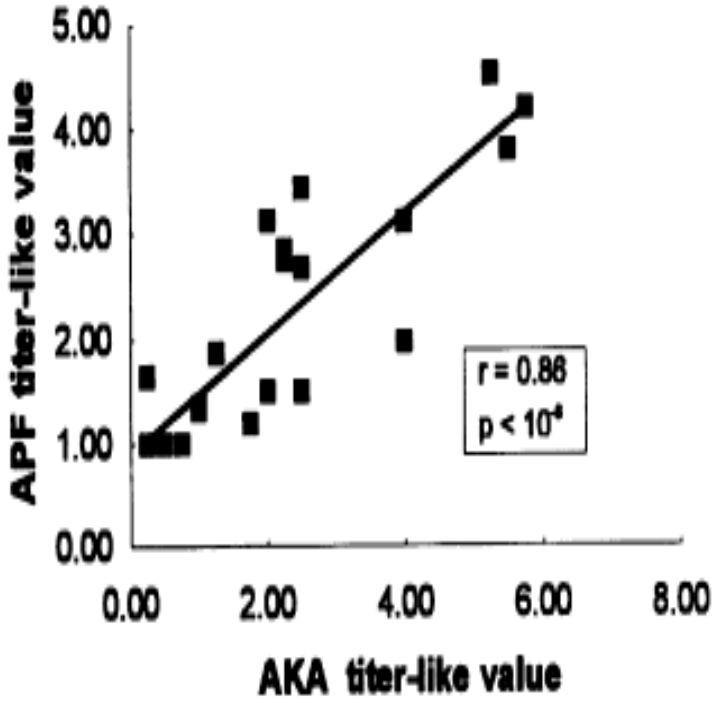
http://www.novusbio.com/Filaggrin-Antibody_NBP1-87527.html



Fillaggrin

Anti- Fillaggrin and APF are the same antibodies

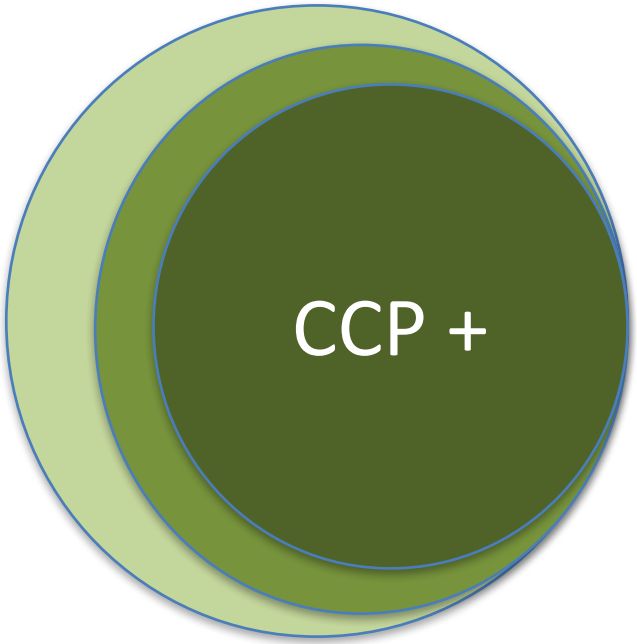




Sebbag et al. The perinuclear factor and the so-called anti-keratin antibodies are the same rheumatoid arthritis specific antibodies J Clin Invest 1995; 95:2672-2679

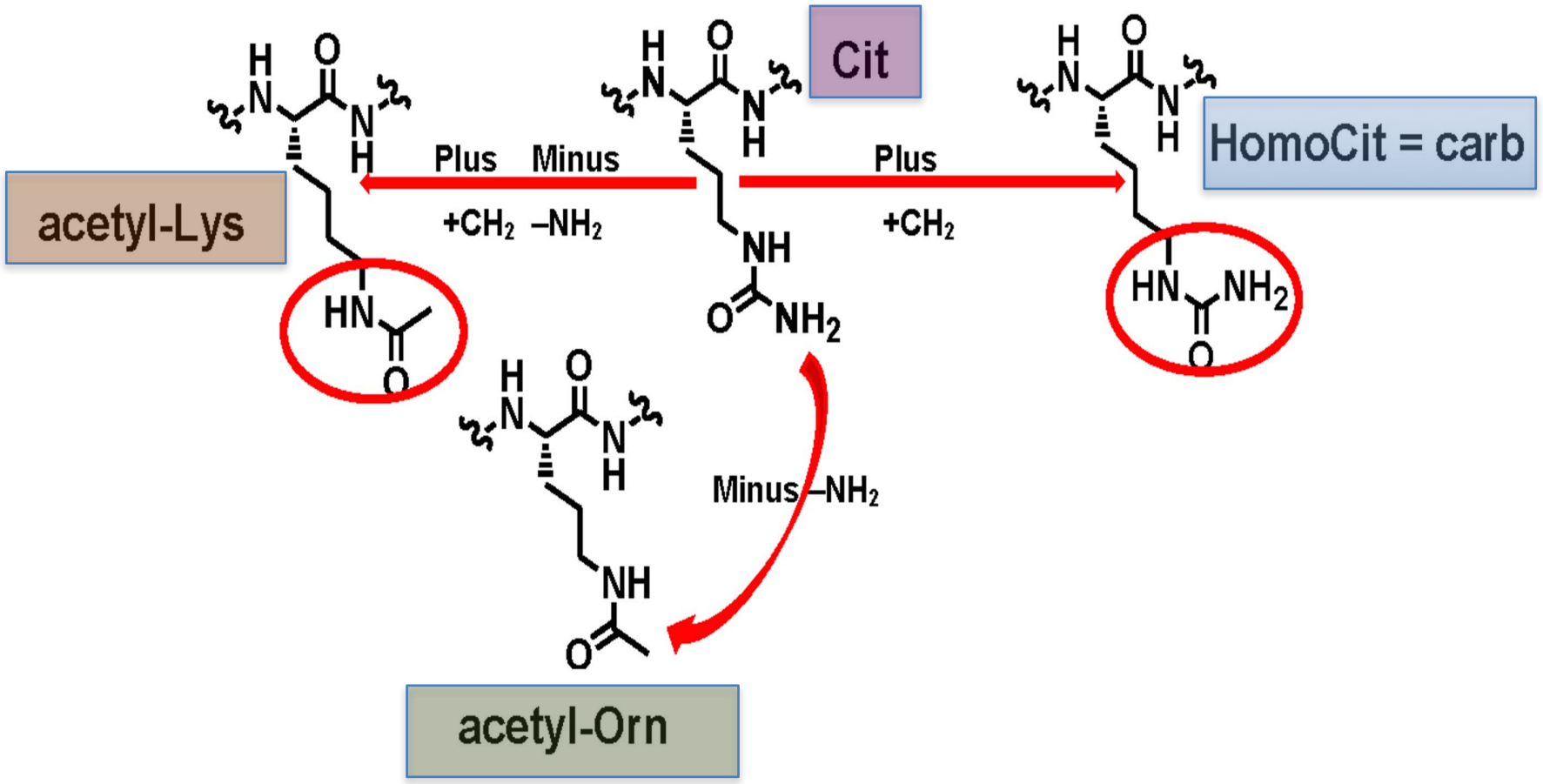
Several epitopes are recognized by anti-citrullinated protein antibodies

Filaggrin 48–65
Fibrinogen B 246–267
Fibrinogen
Fibrinogen A 211–230
Fibrinogen A 582–599
Fibrinogen A 556–575
Fibrinogen A 616–635
Vimentin
H2B/a 62–81
H2A/a 1–20
Histones 2A
Histones 2B
Clusterin 221–240
Clusterin 231–250
Biglycan 247–266
Enolase 1A 5–21
Vimentin 58–77
Apolipoprotein E
Apolipoprotein E 277-296



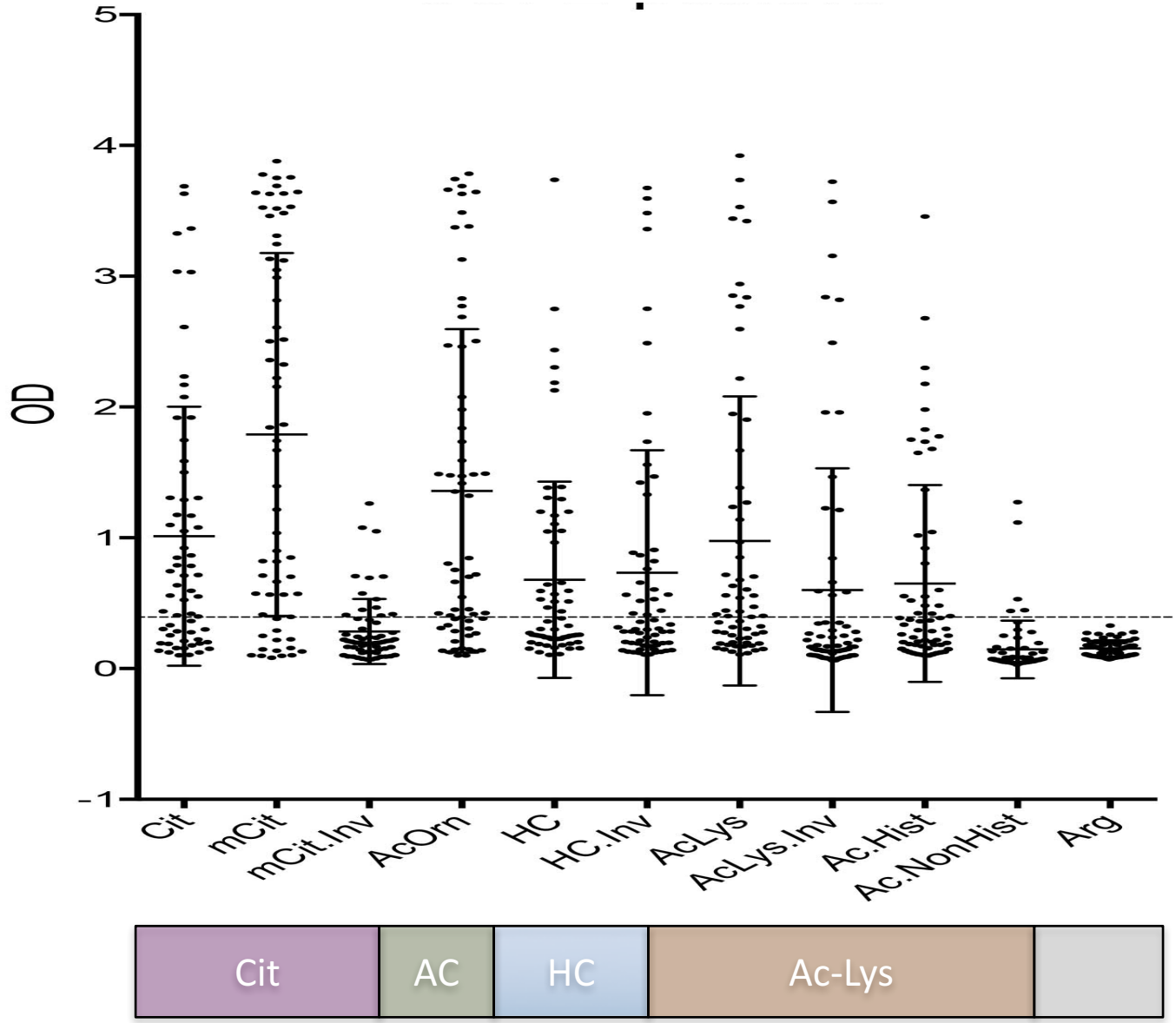
CCP is a screening test covering several different anti-citrullinated protein antibody responses

Alternative protein modifications

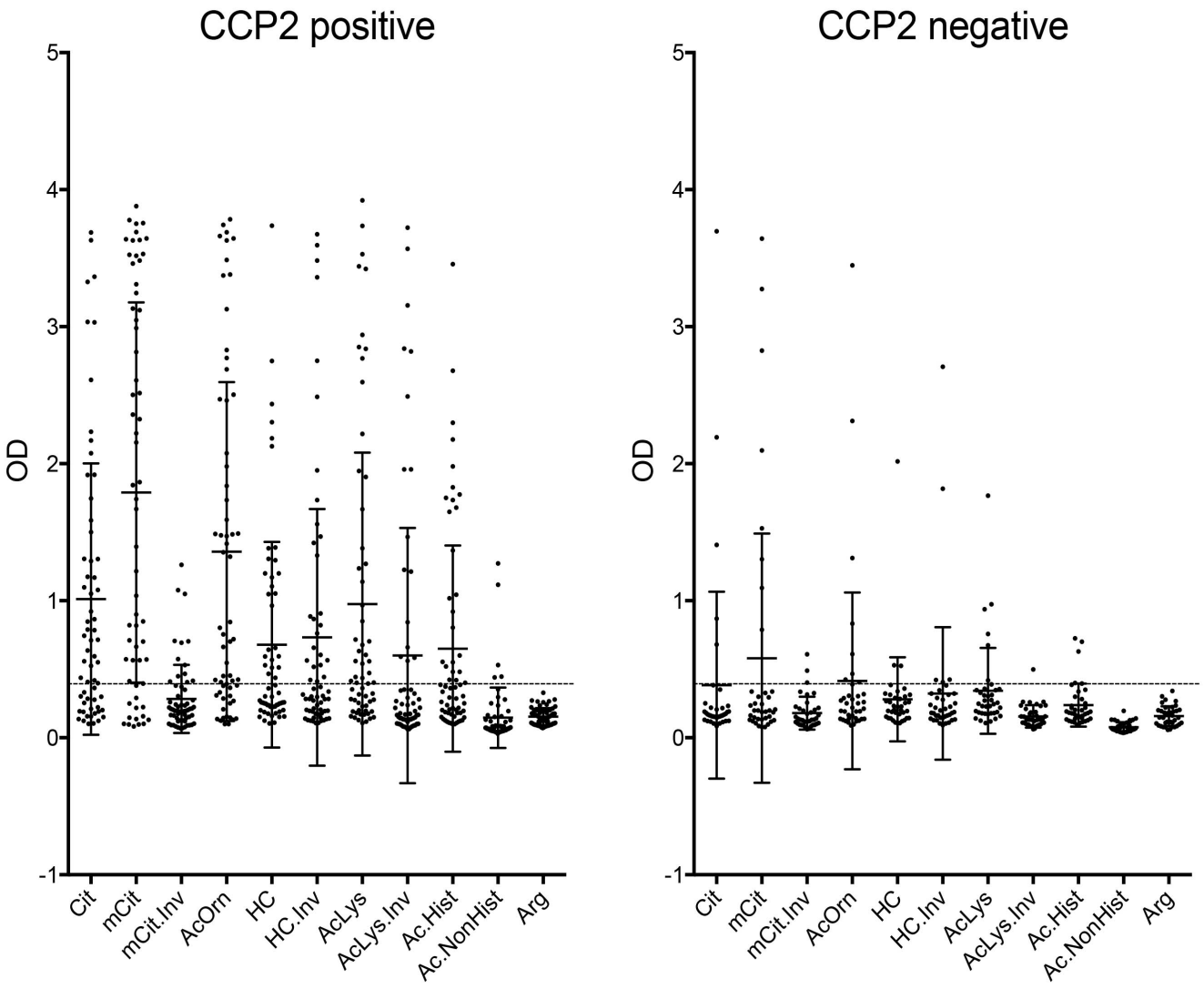


Figueiredo C et al., Ann Rheum Dis 2016

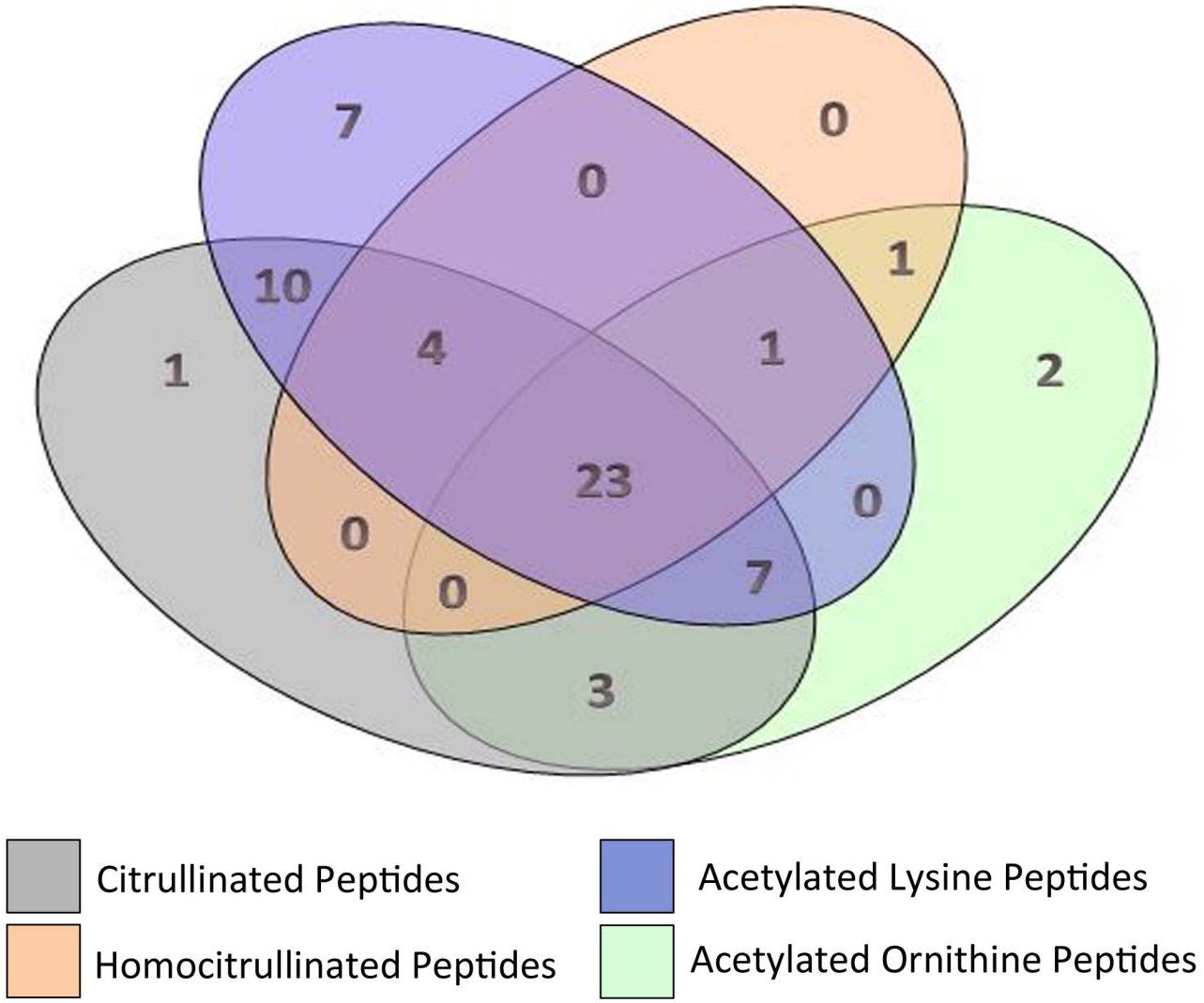
Anti-modified protein Ab response



CCP and anti-modified protein Ab response



Interactions between anti-modified protein Ab

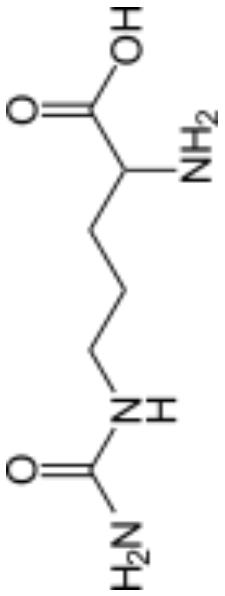


Figueiredo C et al., Ann Rheum Dis 2016

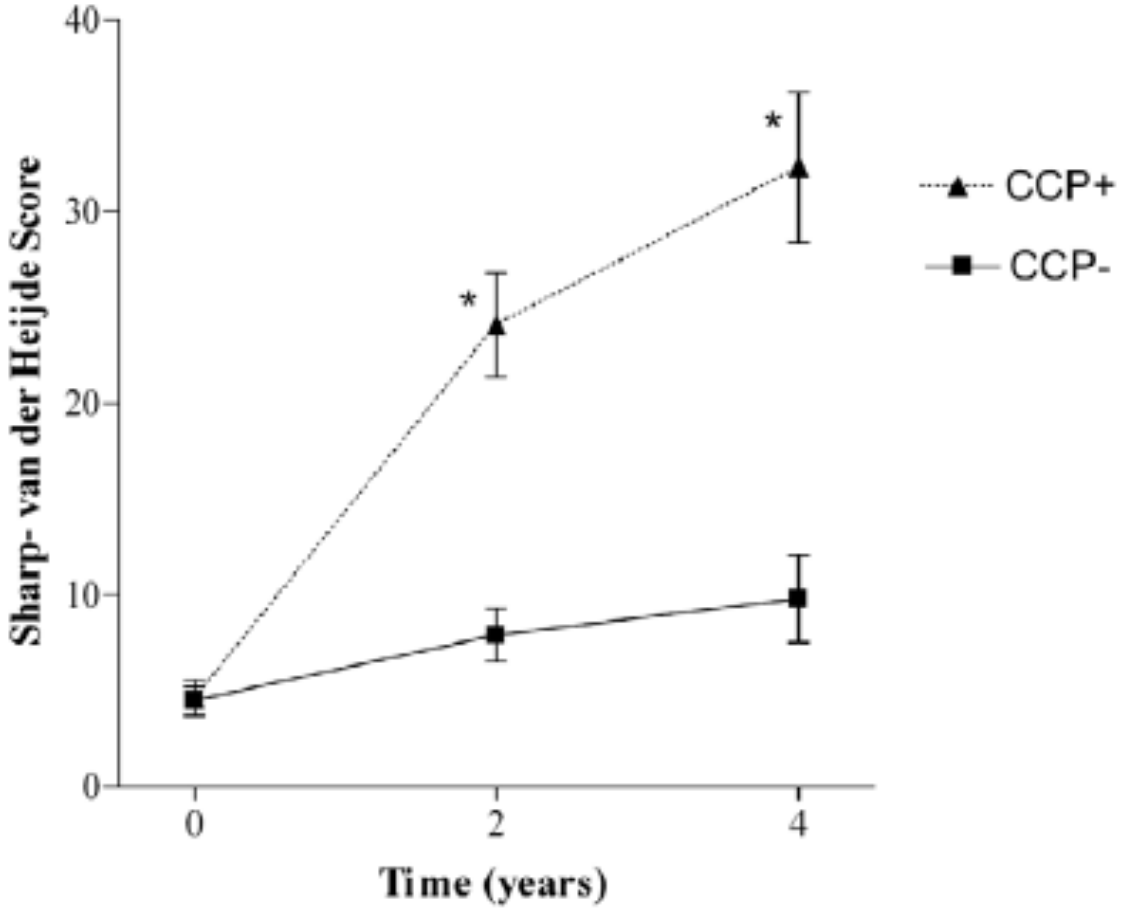
TOPICS

1. ACPA and AMPA
2. Pathophysiologic role of ACPA and RF on the bone
3. ACPA/AMPA and disease course of RA
4. DMARDs and ACPA

ACPA: More Severe Disease Course



Citrullin

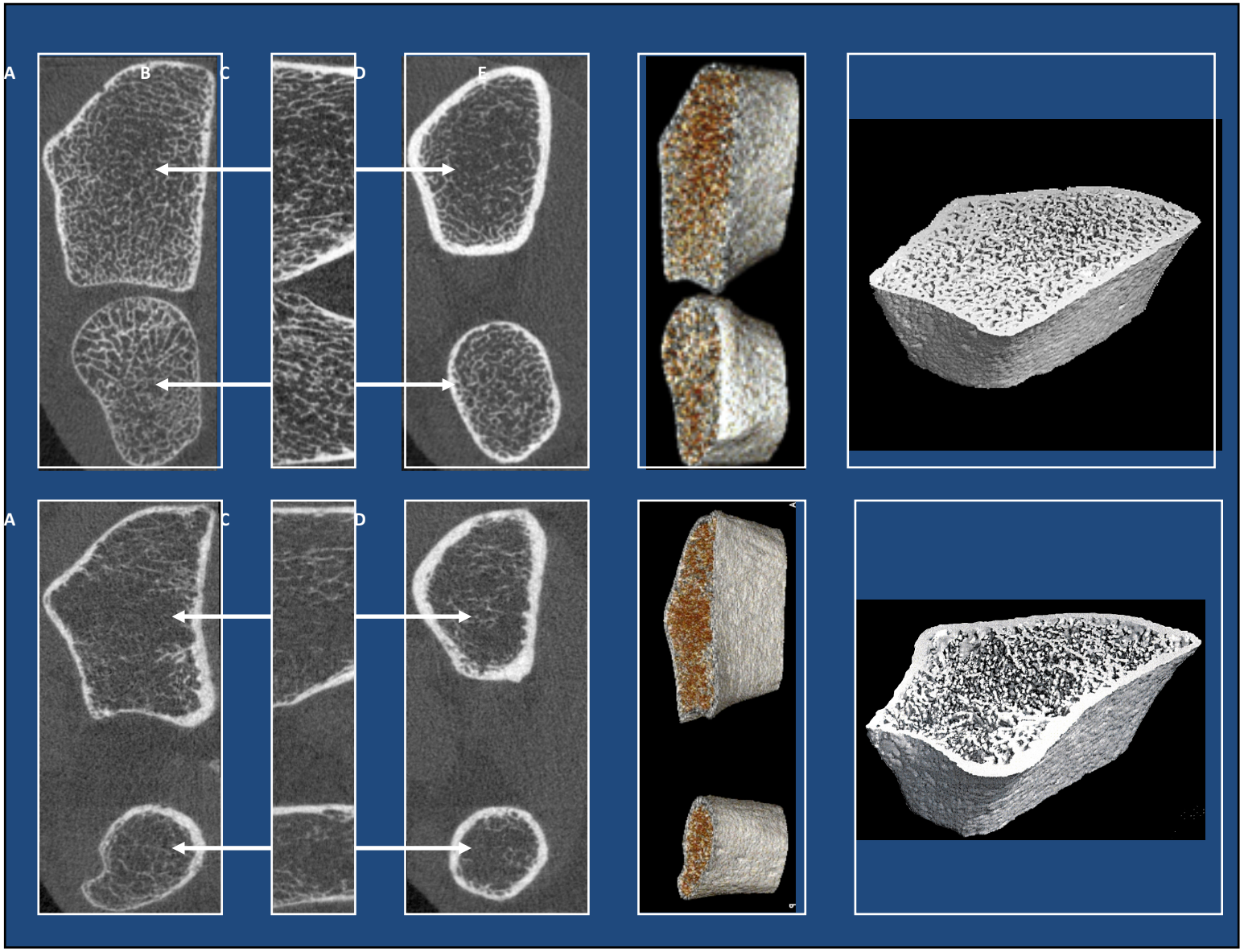


Van der Helm-van Mil AH, et al. Arthritis Res Ther 2005;7(5):R949-58.

More severe disease in ACPA+ RA patients

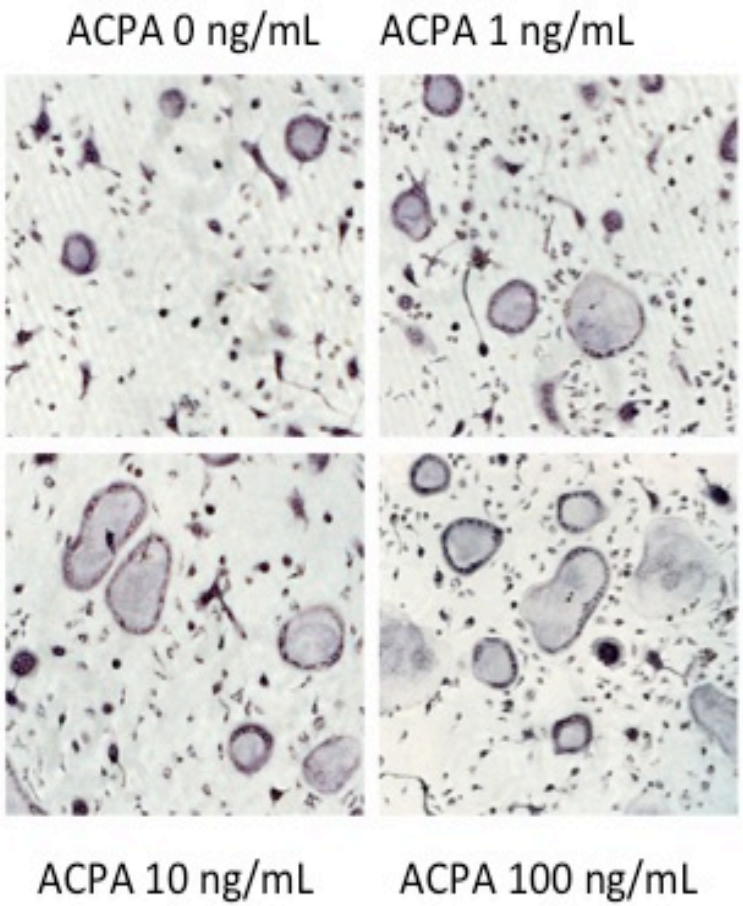
RA[-]

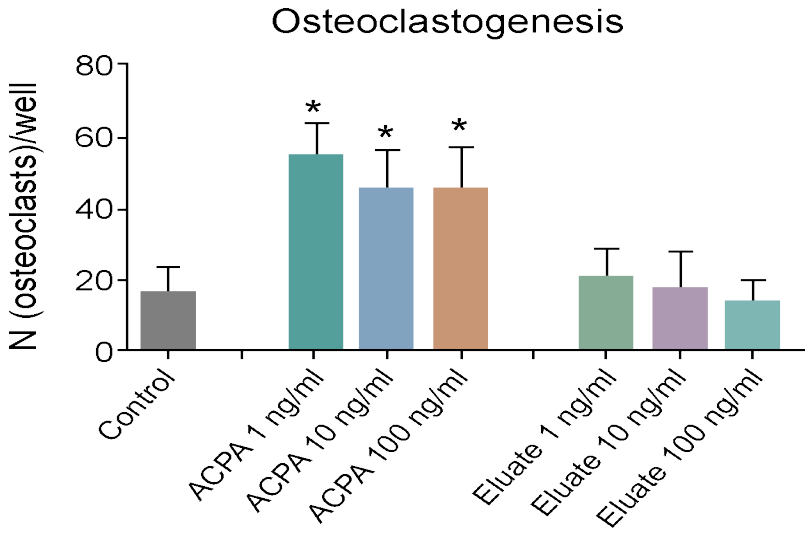
RA[+]

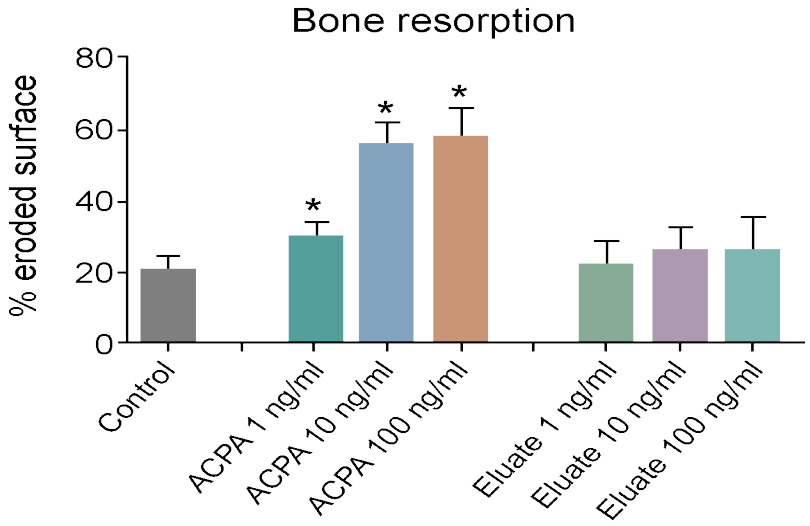


Kocijan et al. , Ann Rheum Dis 2013

ACPA induce OC differentiation

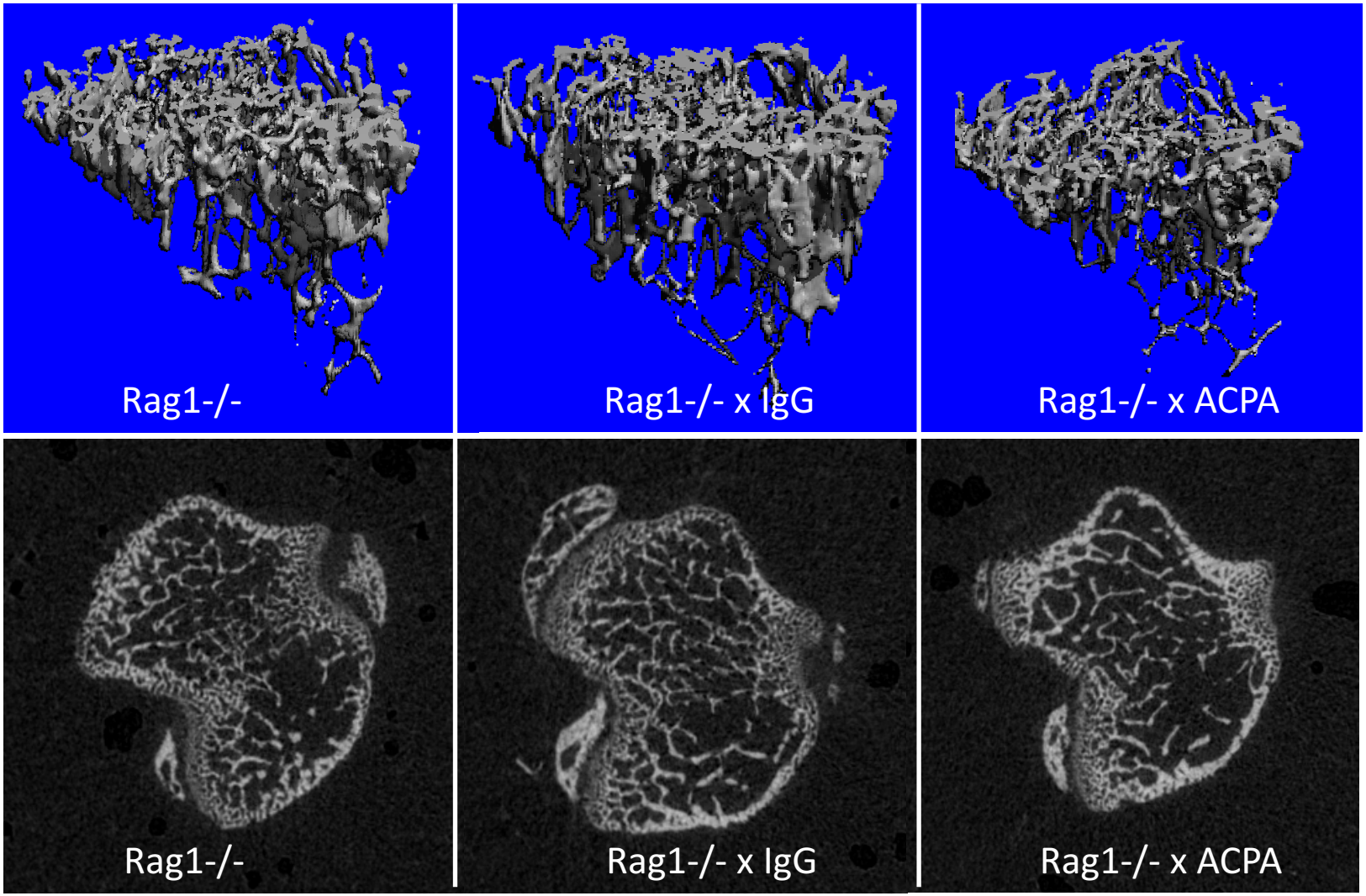




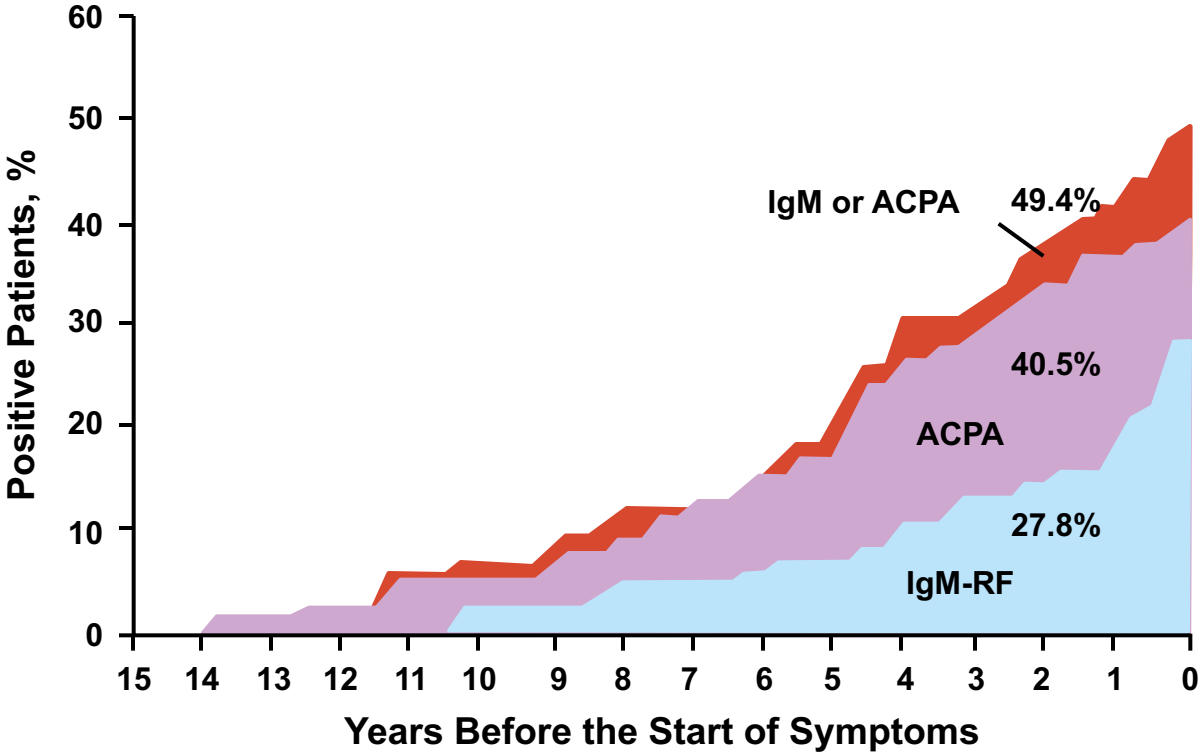


Harre U, et al. J Clin Invest 2012;122:1791–802.

Induction of Bone Loss by ACPA in mice



ACPA and RF precede RA



- ACPAs and RFs in patients appear many years prior to RA onset[1]
- IgA RFs also appear in patients years prior to clinical symptoms[2]

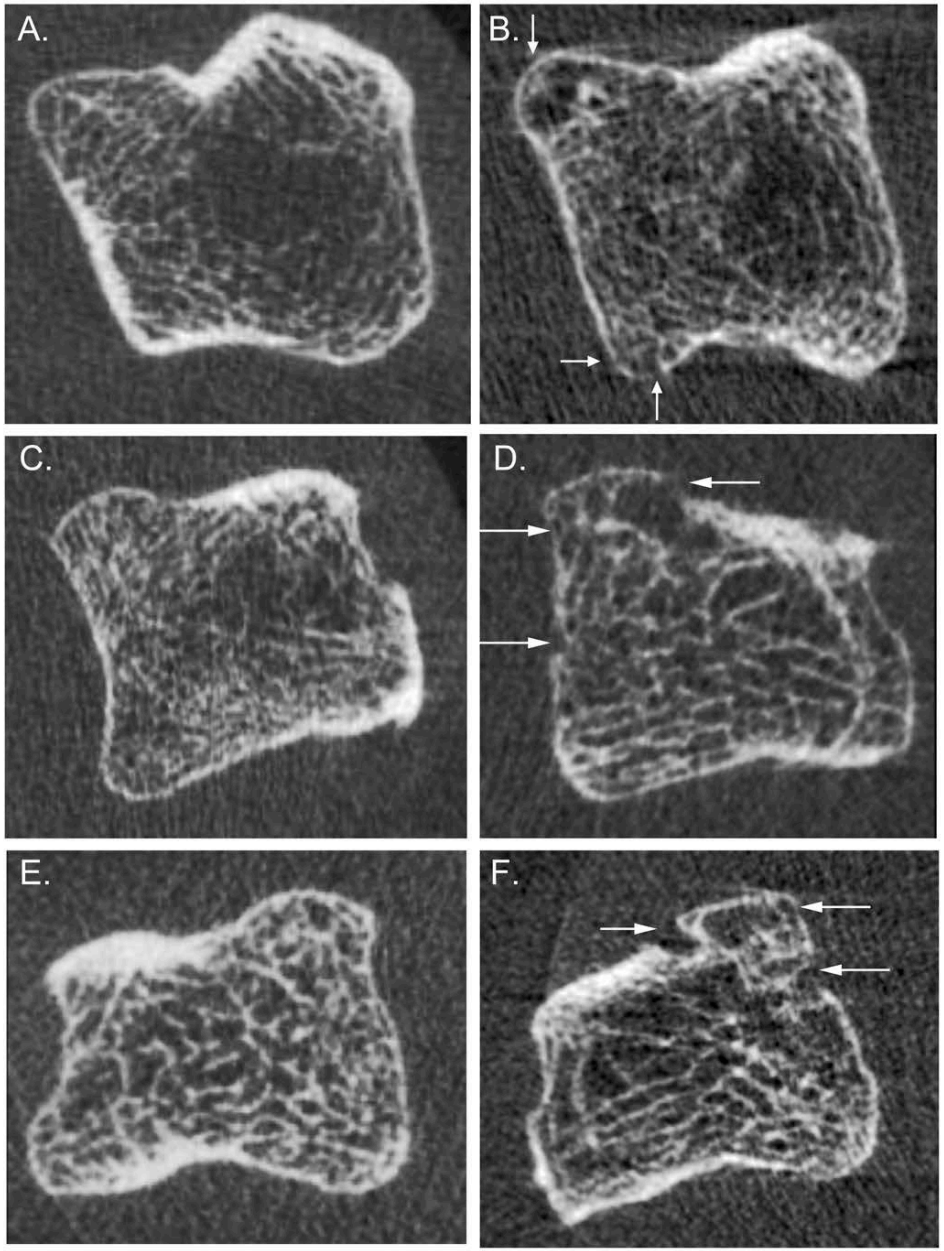
Nielen MM, *et al. Arthritis Rheum.* 2004;**50**:380–6;
Rantapää-Dahlqvist S, *et al. Arthritis Rheum.* 2003;**48**:2741–9.

Bone structure is altered in

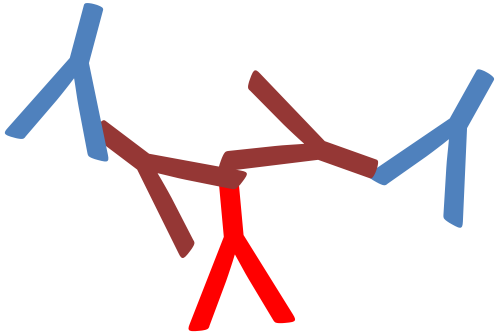
ACPA- positive non-arthritic individuals

as compared to

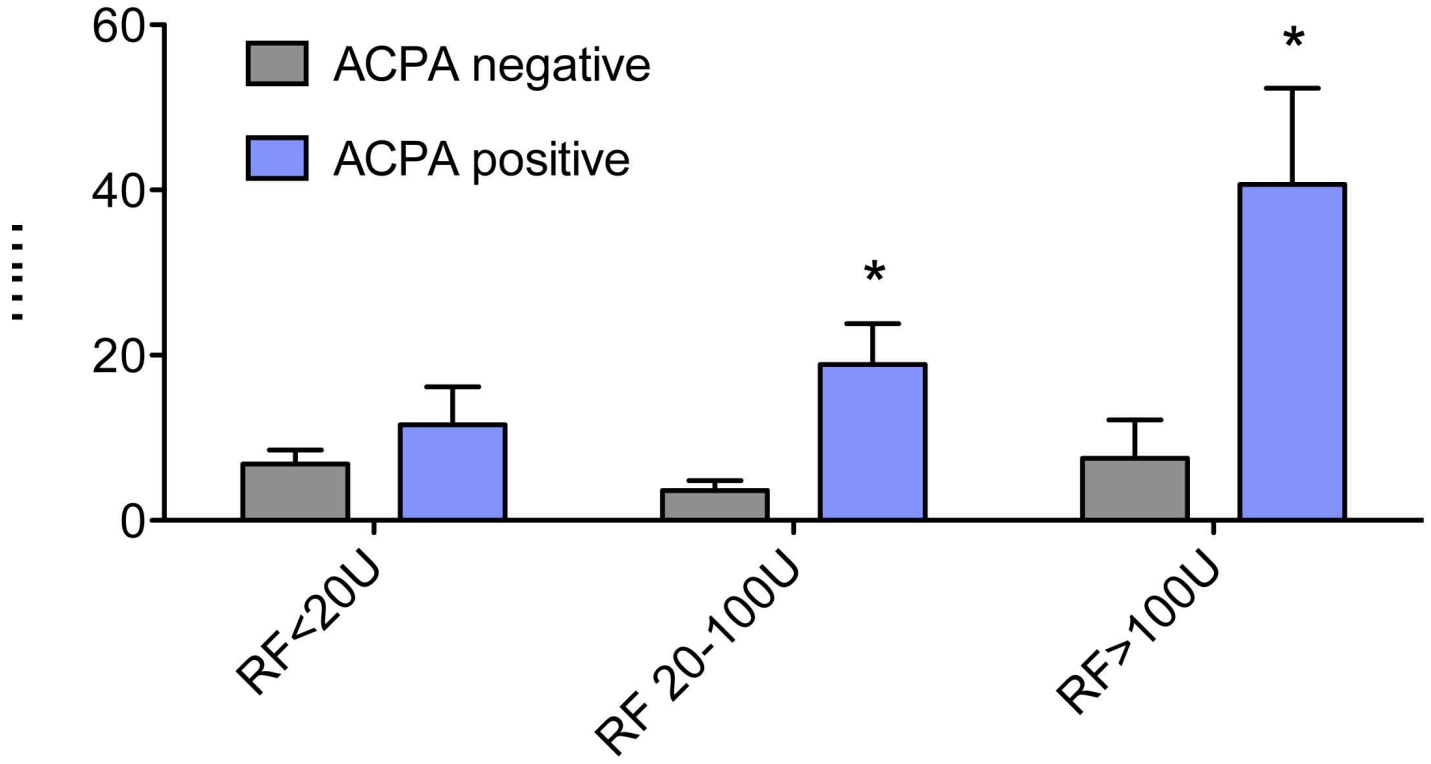
ACPA-negative controls



Kleyer et al, Ann Rheum Dis 2013

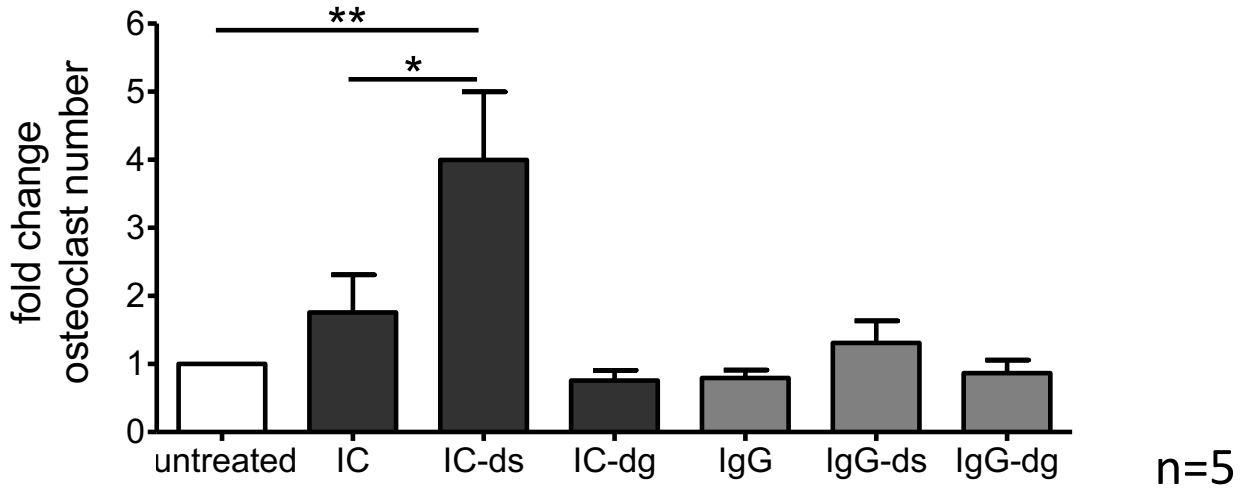


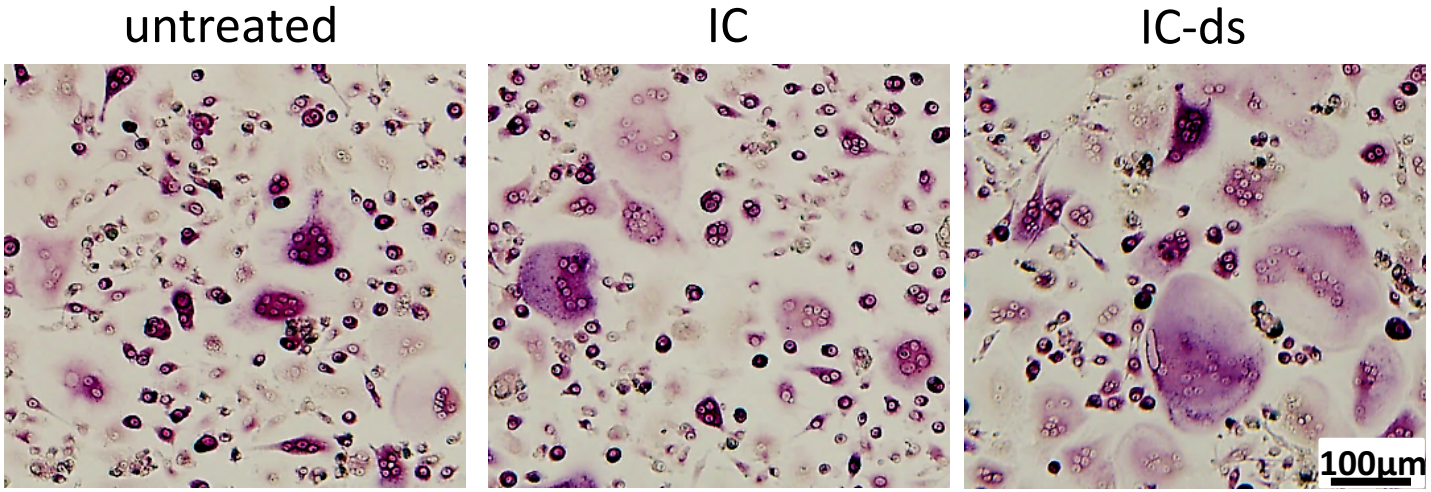
Interaction between ACPA and RF in RA mediated bone loss



Hecht C et al., Ann Rheum Dis 2014

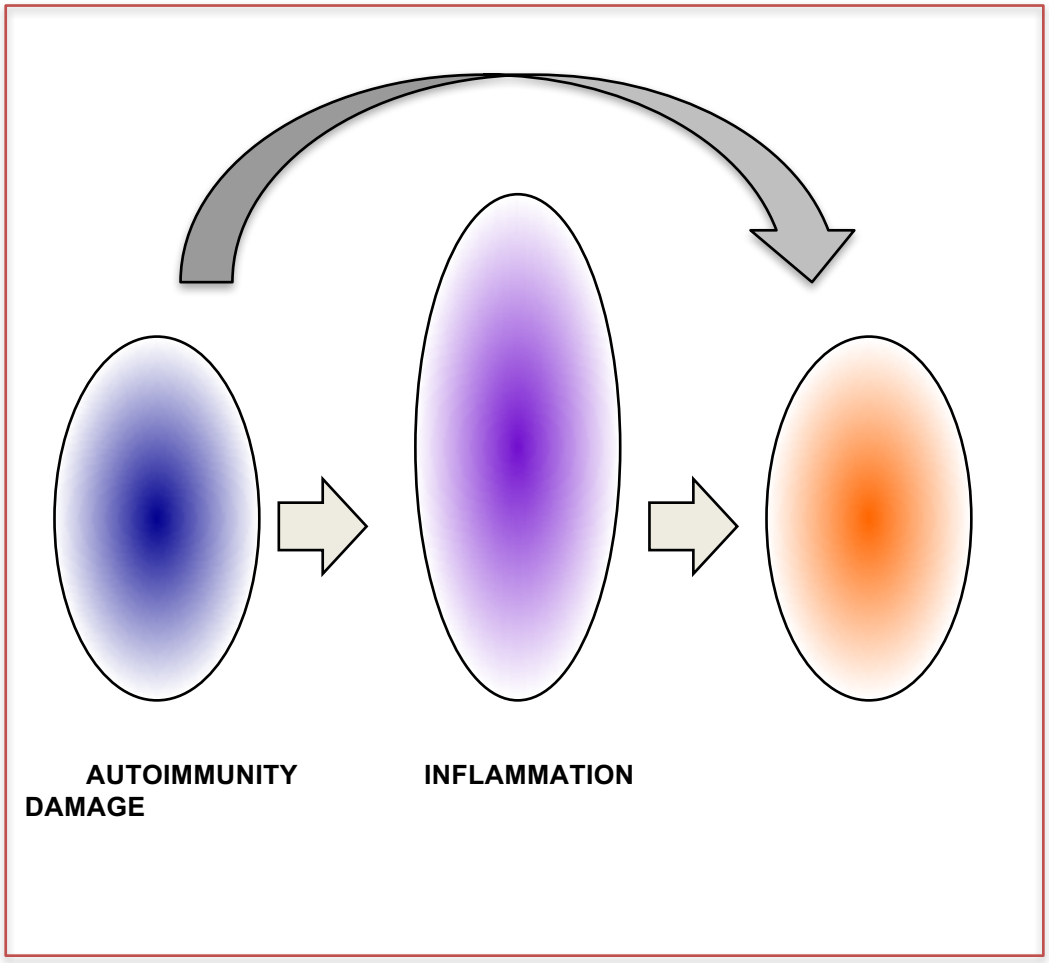
Desialylated IgG complexes stimulate OCs





Harre U et al. Nat Comm 2015

New and traditional concept of structural damage



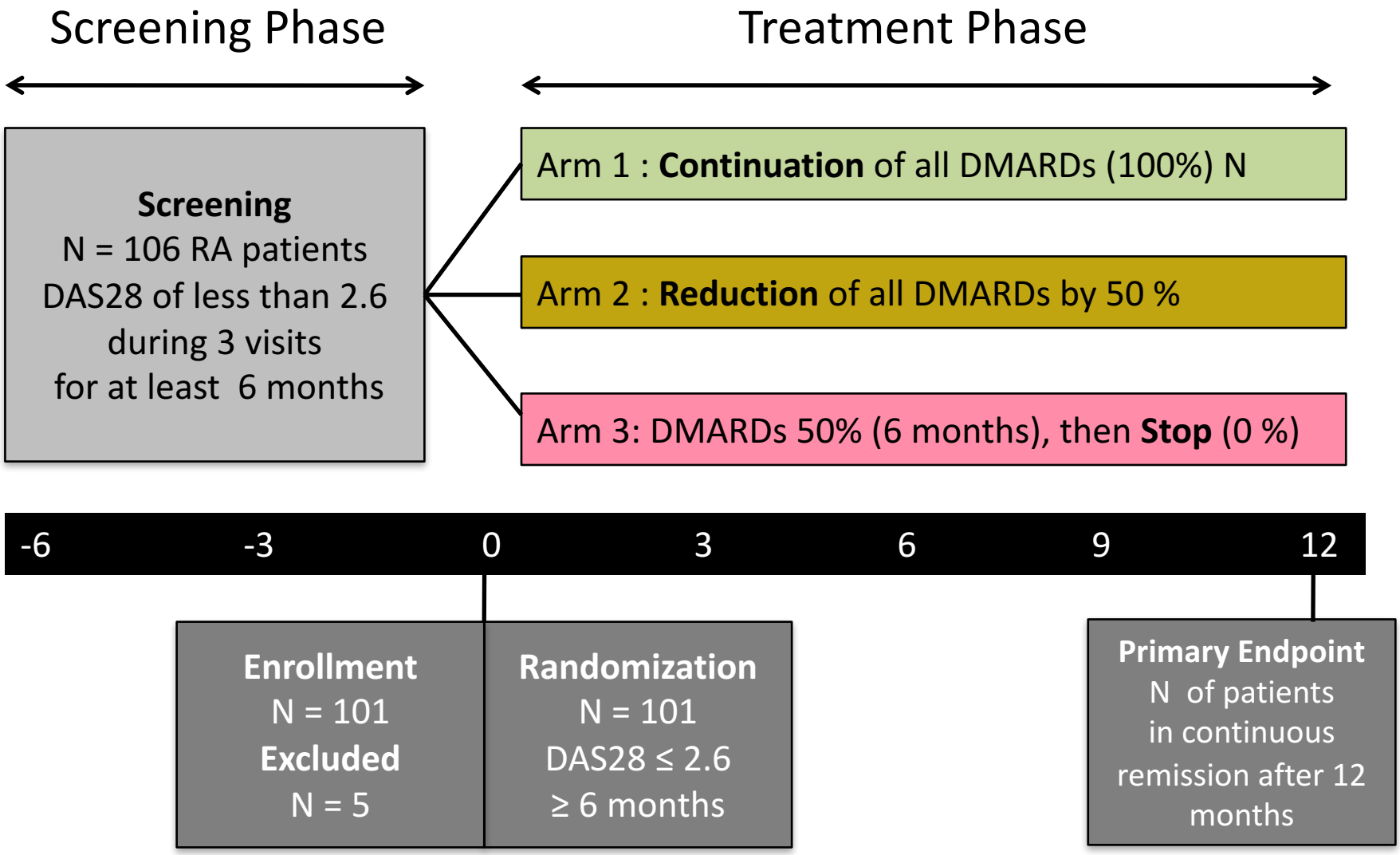
- Immune complexes such as rheumatoid factors trigger bone loss by Fc-mediated stimulation of osteoclasts
- Autoantibodies against citrullinated proteins (ACPA) induce osteoclast differentiation
- Bone erosion in RA relies on the stimulation of bone-resorbing osteoclasts by AAB (early and late) and cytokines (late)

TOPICS

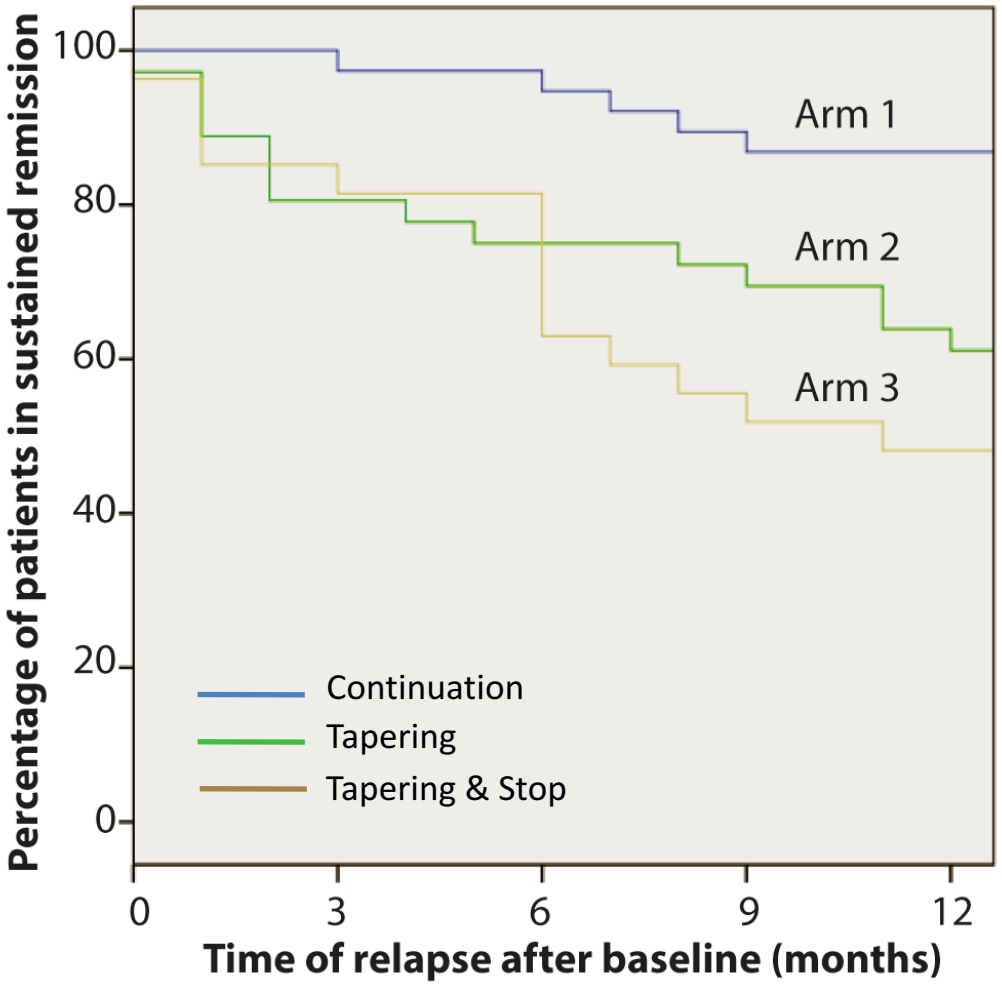
1. ACPA and AMPA
2. Pathophysiologic role of ACPA and RF on the bone
3. ACPA/AMPA and disease course of RA
4. DMARDs and ACPA

RETRO Study

Real-life Medicinal Products Act conform study



Remission Status over 1 year



66.3% remained in remission over of 12 months, and **33.7% relapsed**

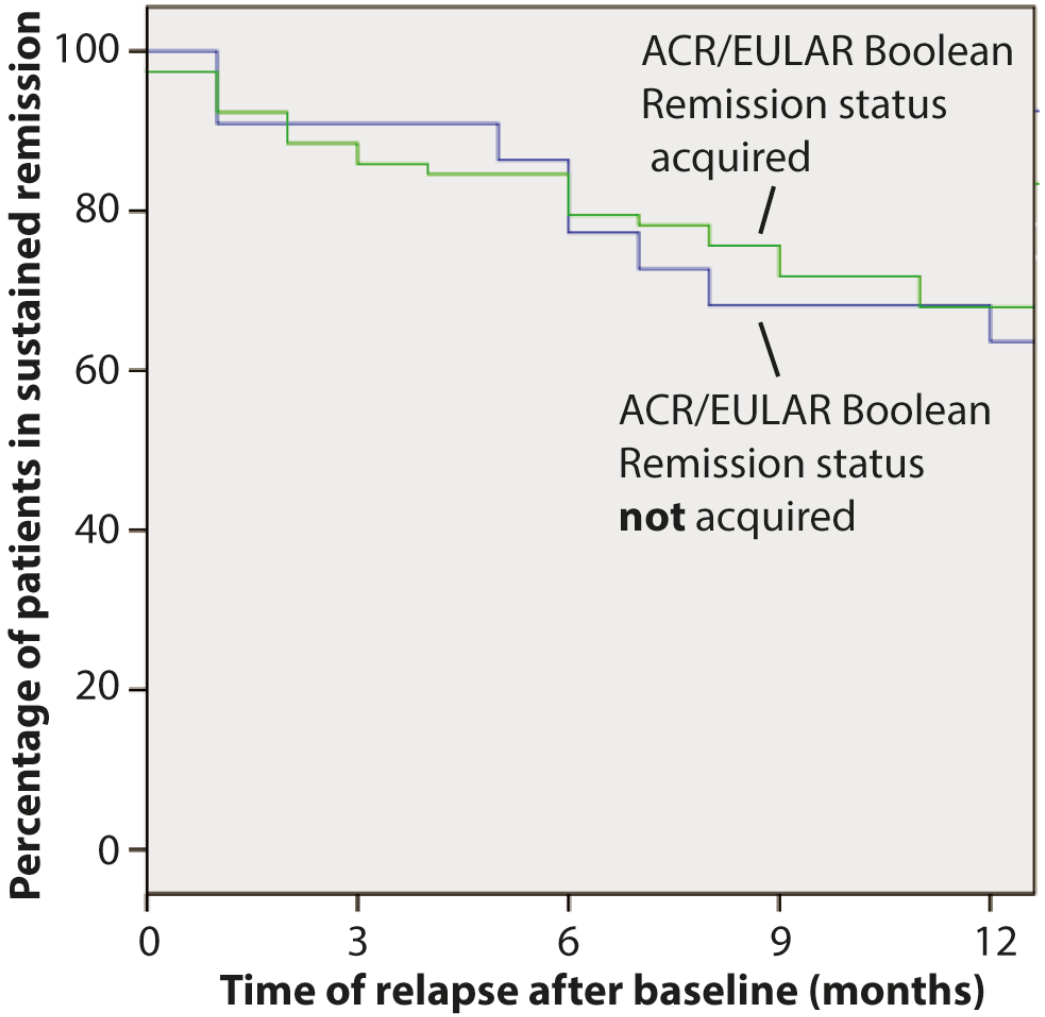
Prevalence of disease relapse was **15.8%** in arm 1 and significantly higher in arm 2 (**38.9%**;, *p*=0.036) and arm 3 (**51.9%**; *p*=0.003).

44.4% of patients in the two reduction arms relapsed. No significant differences (*p*=0.443) between the tapering and stopping regimen arms were found.

The majority of relapses occurred **within the first 6 months** during the tapering phase.

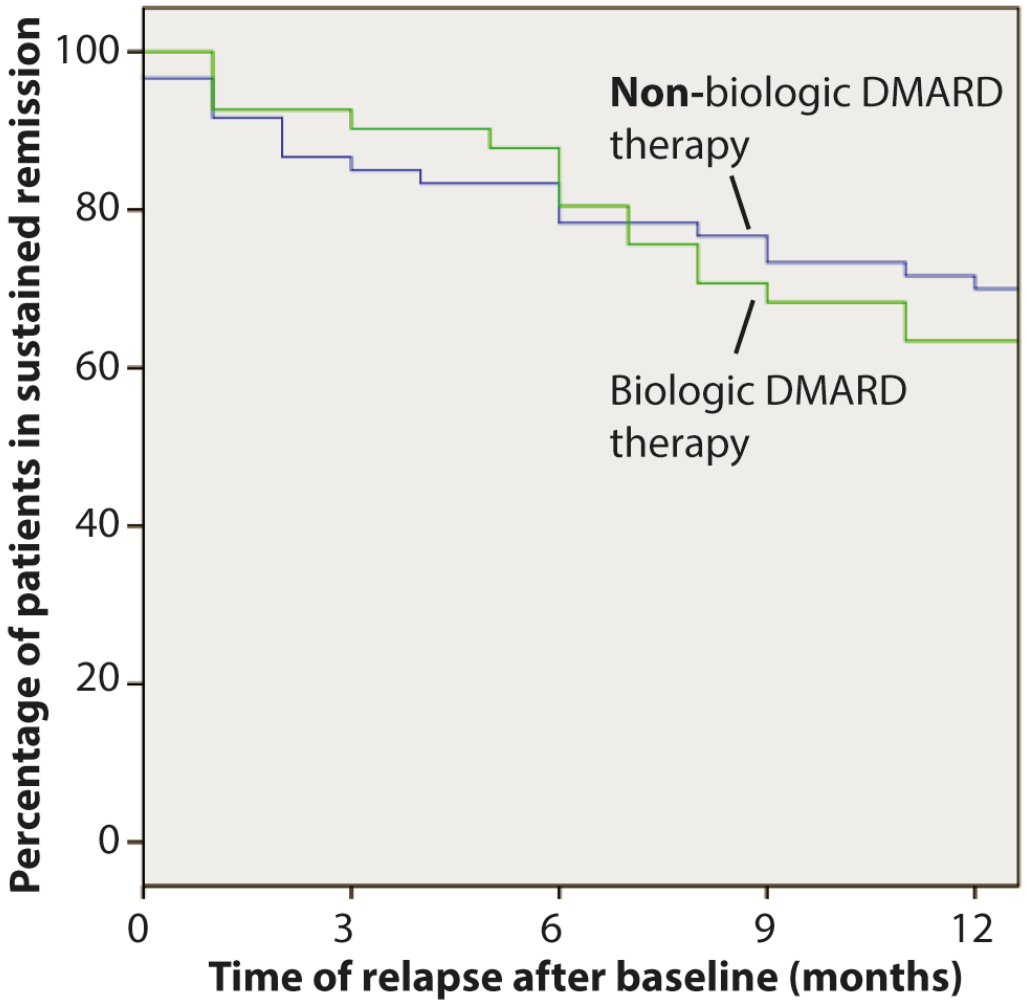
Effect of Boolean Remission on the maintenance of remission status

Boolean Remission vs. No Boolean Remission

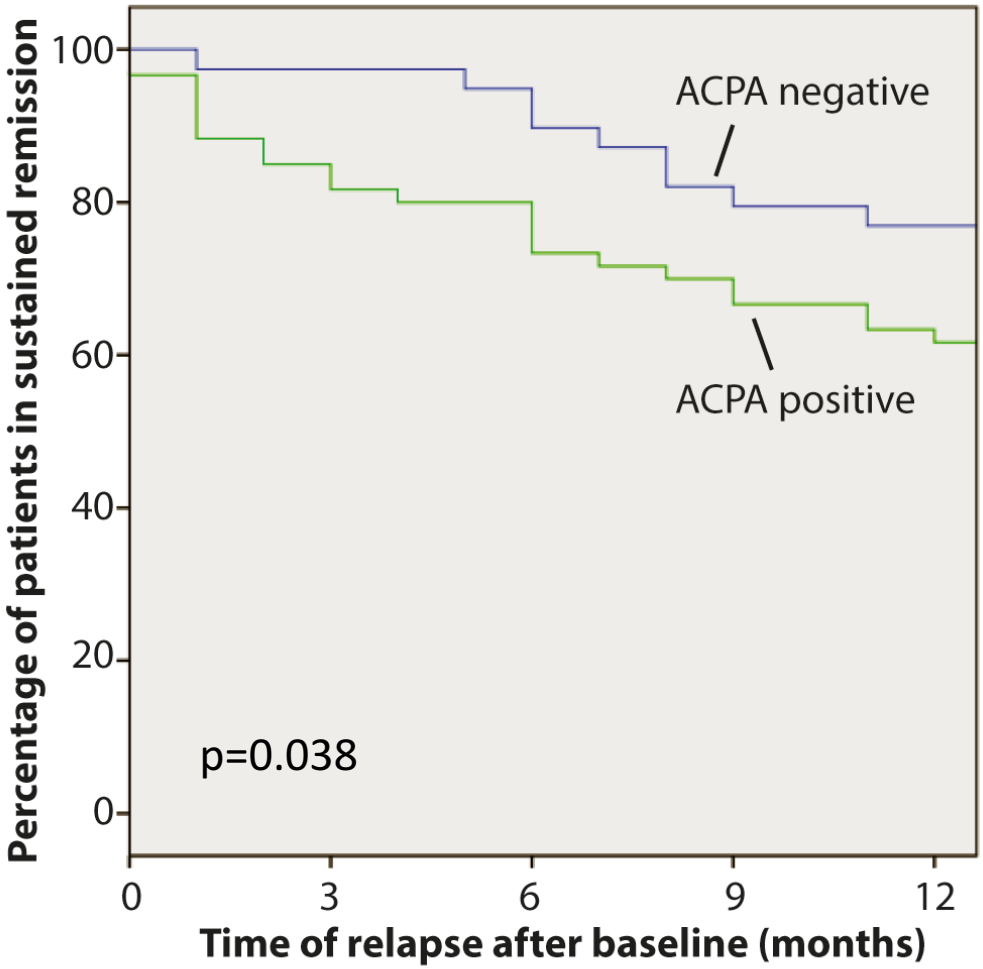


Effect of Biologicals on the maintenance of remission status

Biological
-naive
Patients
vs.
Biological-
Exposed
Patients



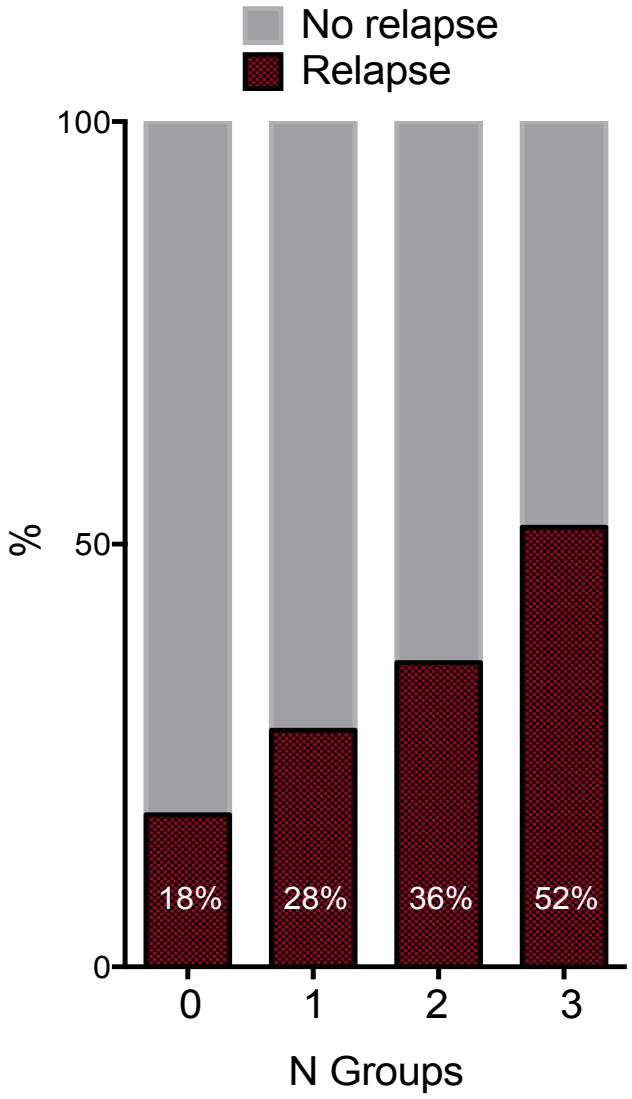
Effect of ACPA positivity on the maintenance of remission status

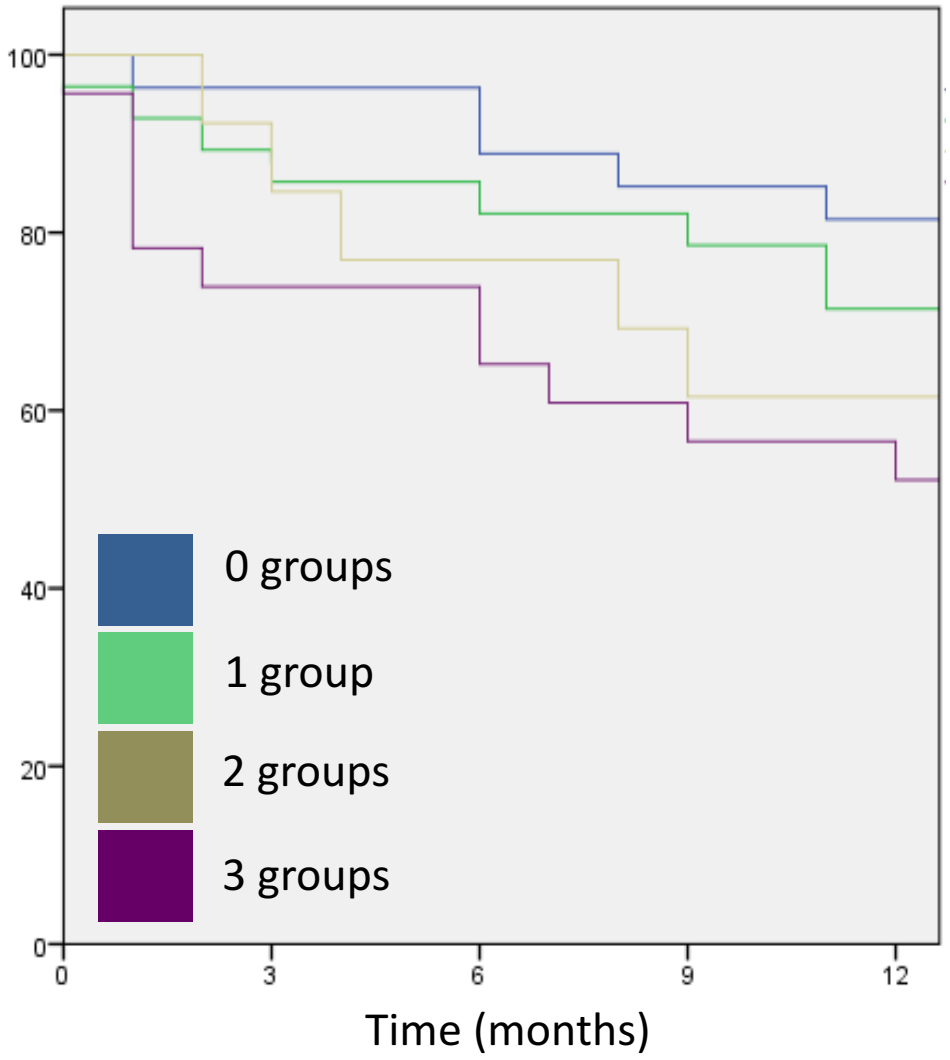


Multivariate logistic regression analysis showed that **ACPA status** was the only factors predicting the risk for recurrence of disease. Disease duration, remission duration, "remission depth" and biological DMARD use were not predictive.

Haschka et al., Ann Rheum Dis 2014

Relapse rate according to the number of anti-modified protein Ab groups (cit, carb,acet)





Risk for relapse according to the number of anti-modified protein Ab groups (cit, carb,acet)

AMPA specificity groups

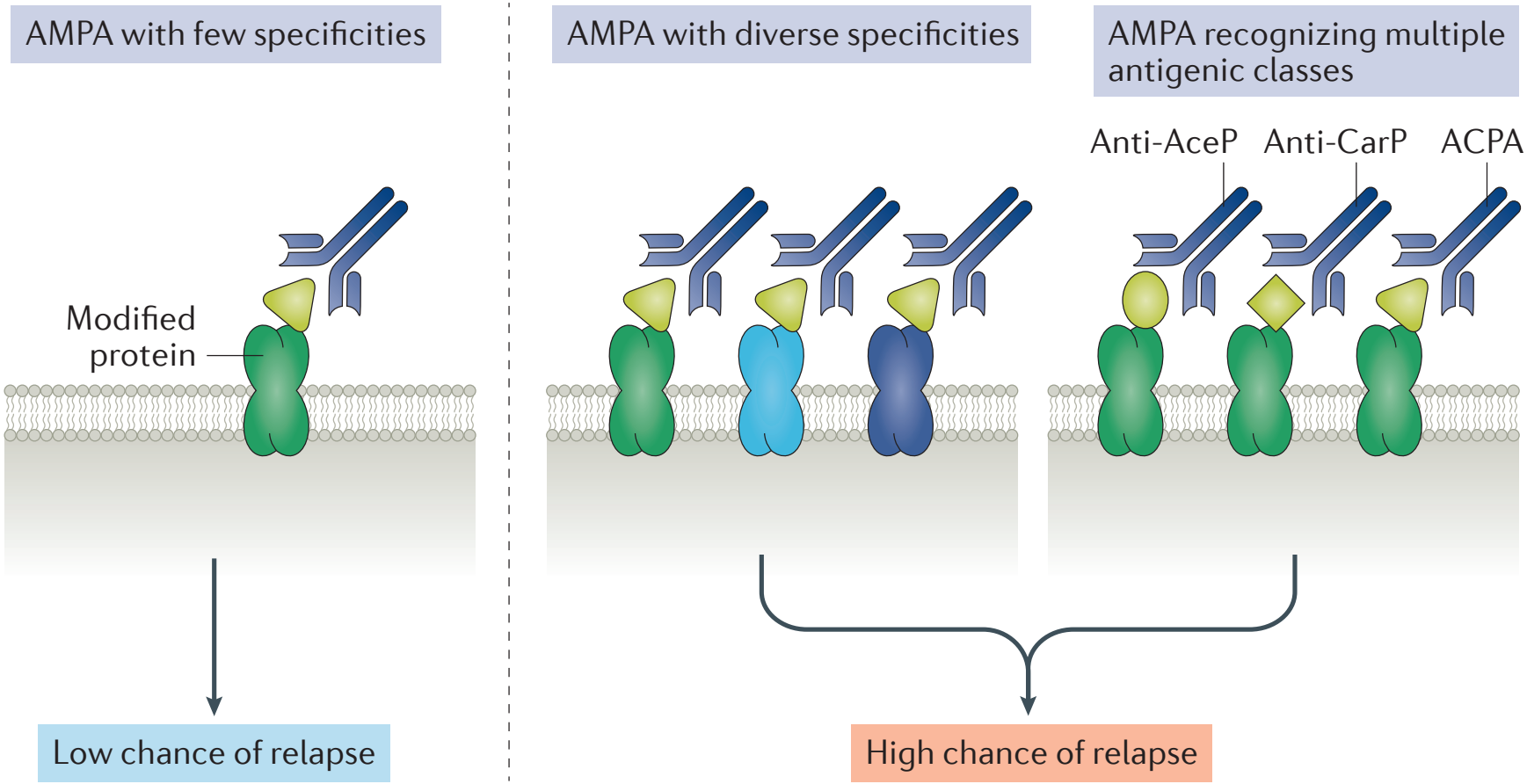
	Continue	Taper	Stop
0	22,2%	23,1% +	30,0%
1	9,1%	40,0%	42,8%
2	25,0%	60,0%	50,0%
3	14,2%	54,5%	83,3%

Figueiredo C et al., Ann Rheum Dis 2016

RETRO

Autoantibody testing to predict response to therapy in RA

Leendert A. Trouw and Rene E. M. Toes



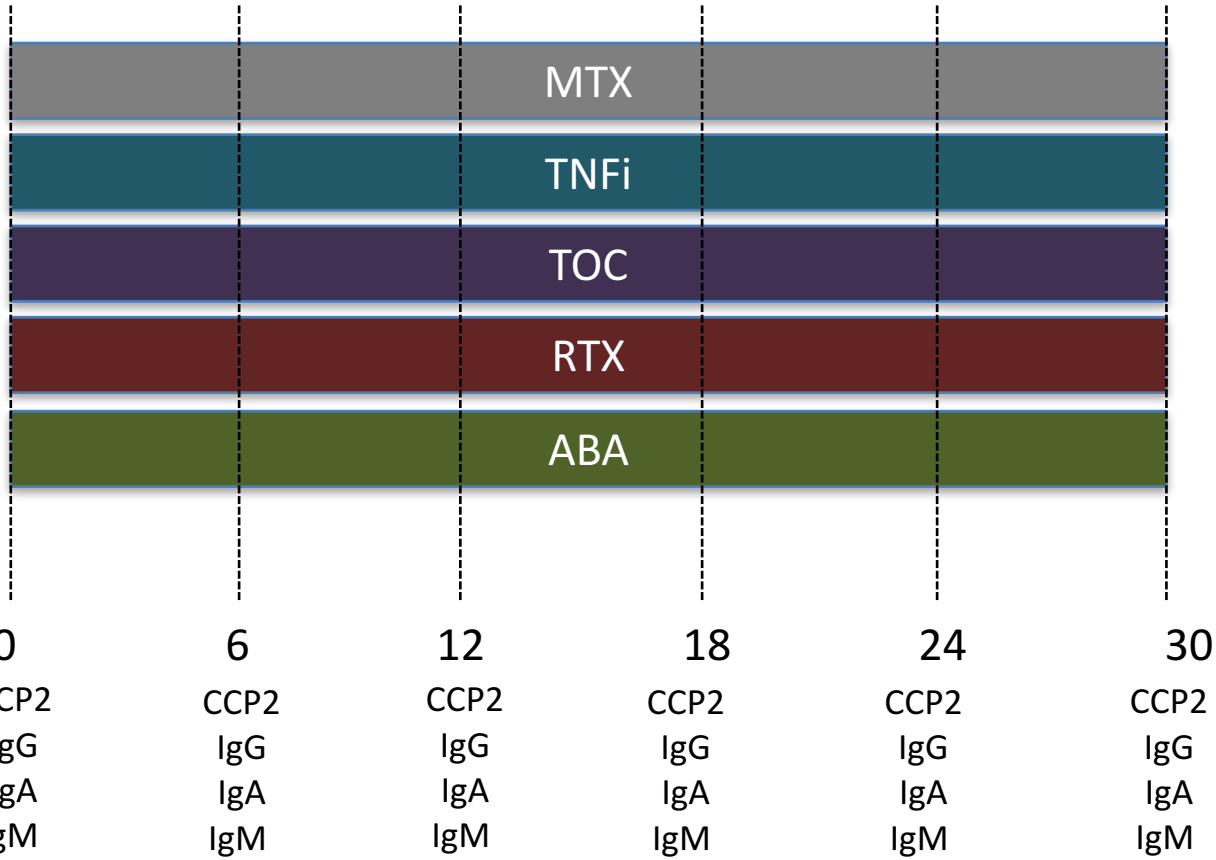
Refers to Figueiredo, C. P. *et al.* Antimodified protein antibody response pattern influences the risk for disease relapse in patients with rheumatoid arthritis tapering disease modifying antirheumatic drugs. *Ann. Rheum. Dis.* http://dx.doi.org/10.1136/annrheumdis-2016-209297 (2016).

TOPICS

1. ACPA and AMPA
2. Pathophysiologic role of ACPA and RF on the bone
3. ACPA/AMPA and disease course of RA
4. DMARDs and ACPA

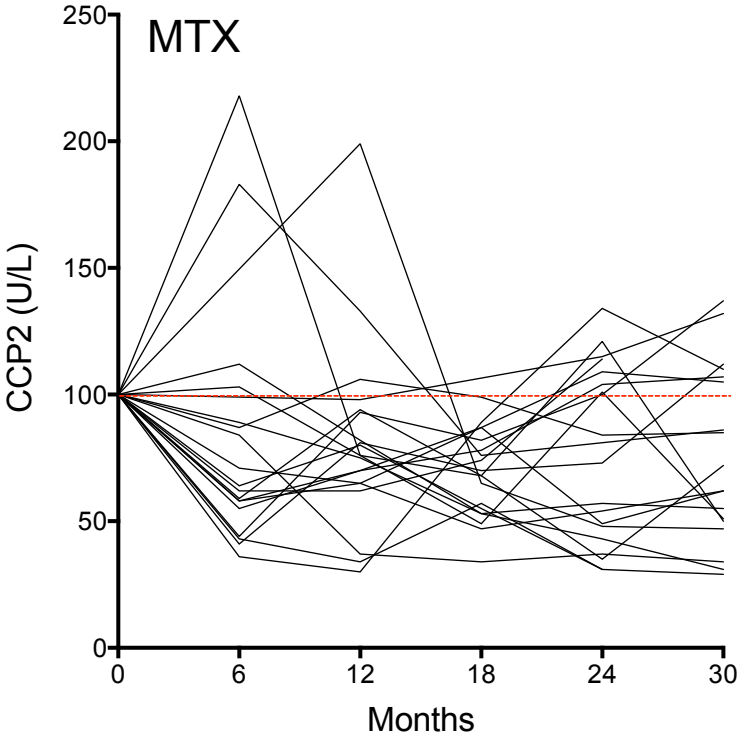
Prospective observational study to test the effects of bDMARDs modalities on CCP2 titers

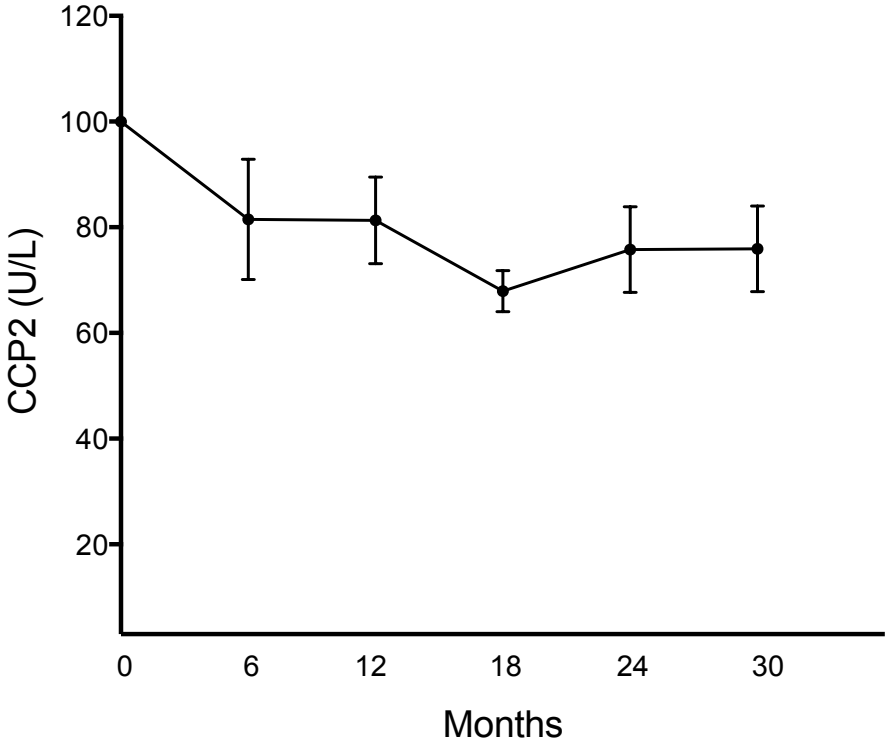
181 patients with active rheumatoid arthritis, fulfillment of the ACR/EULAR 2010 criteria, 100% CCP2 positive



Wunderlich et al., Sem Arth Rheum 2016, in press

Effect of methotrexate treatment

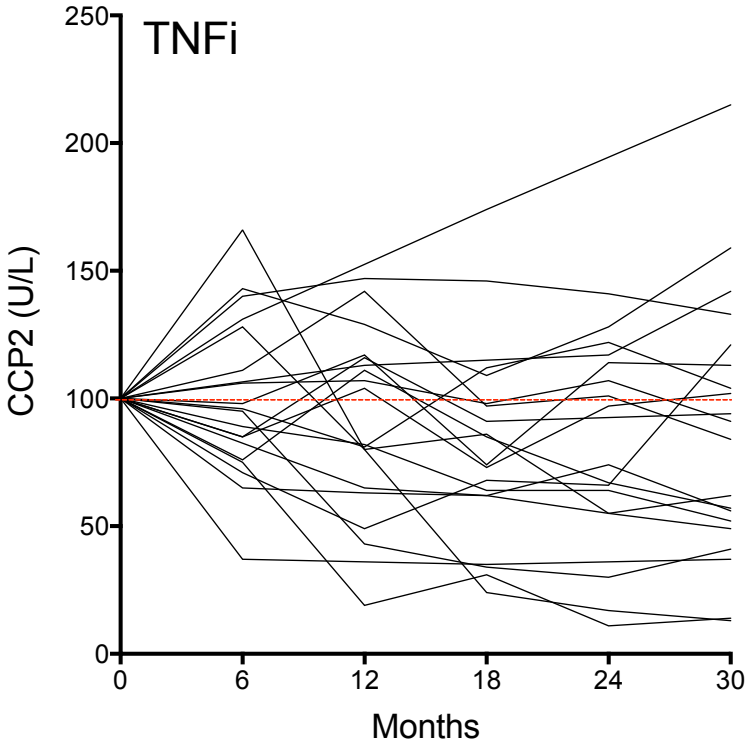


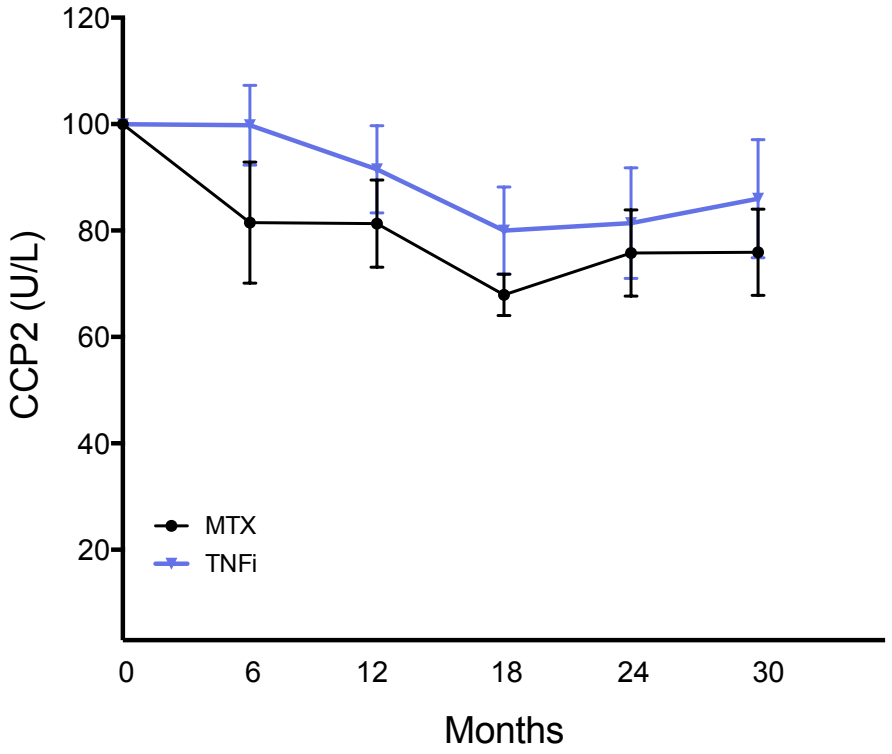


Individual Patients

Group

Effect of TNF inhibitor treatment

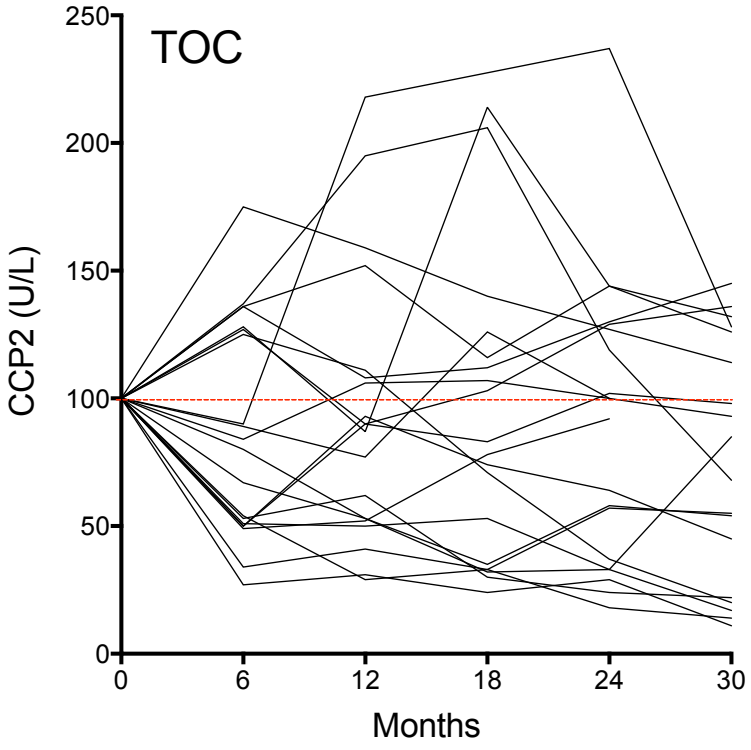


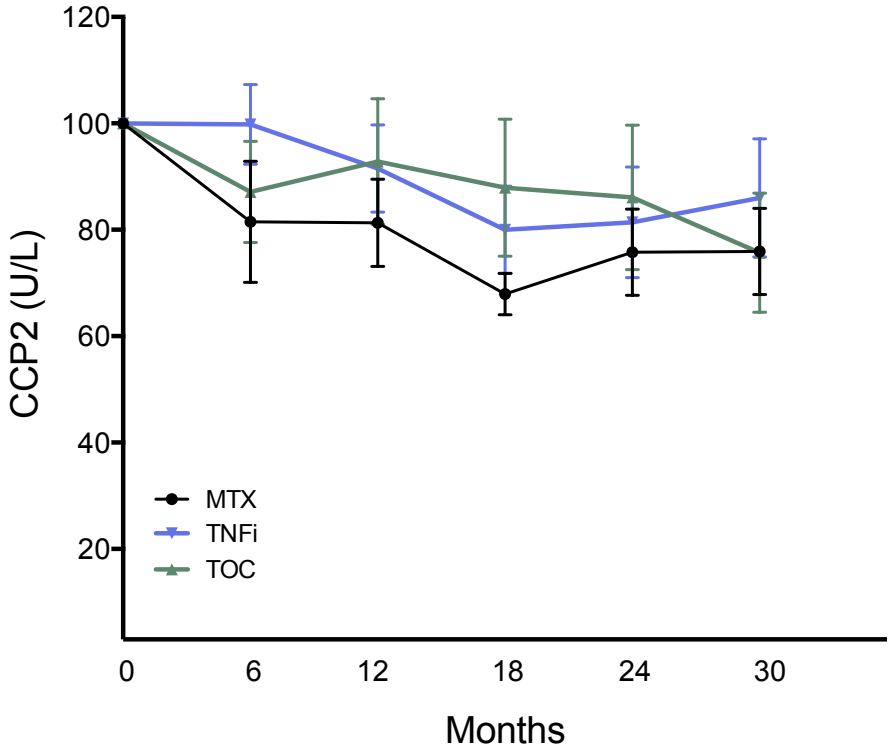


Individual Patients

Group

Effect of tocilizumab treatment

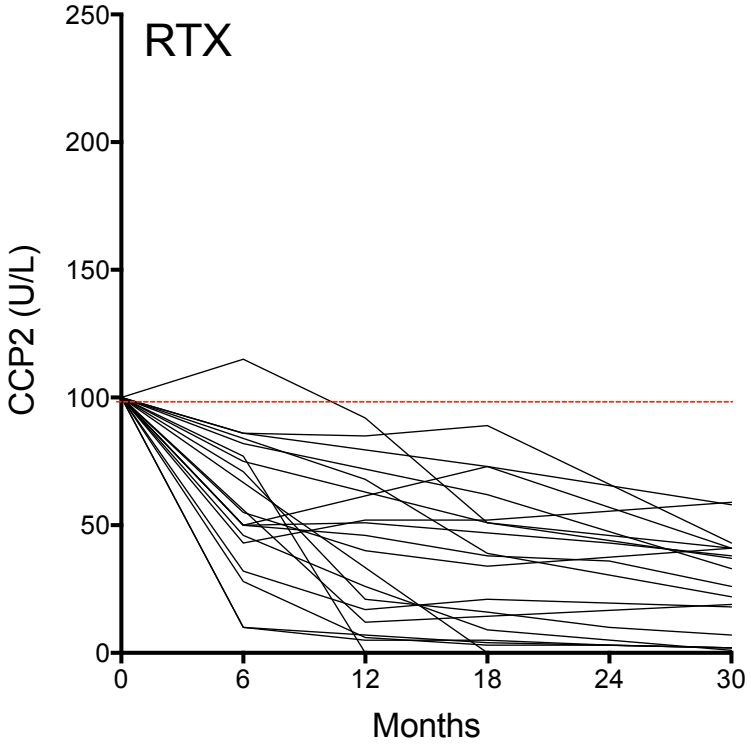


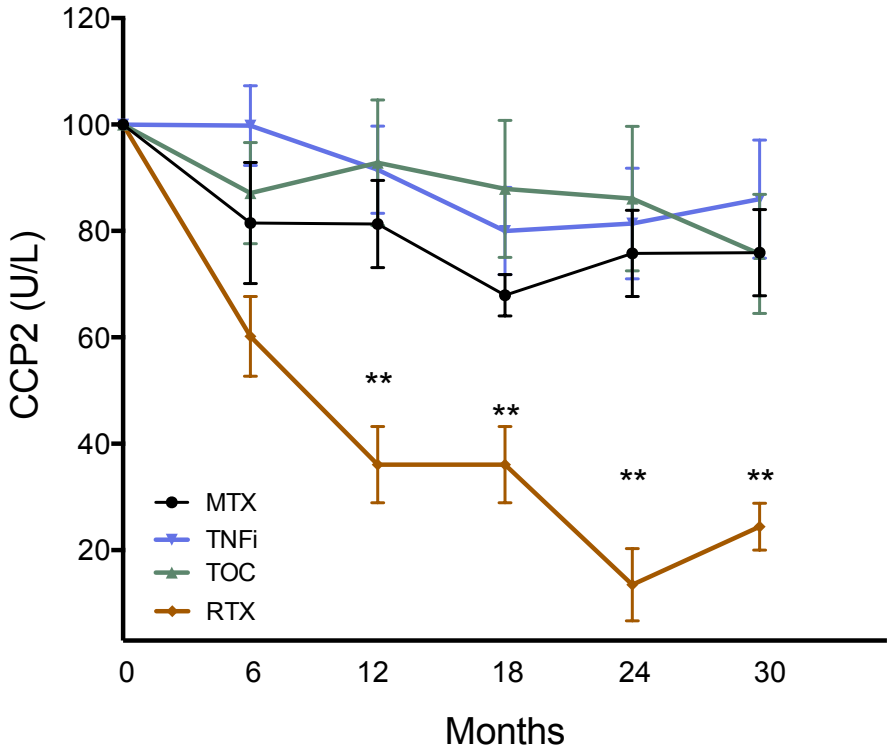


Individual Patients

Group

Effect of rituximab treatment

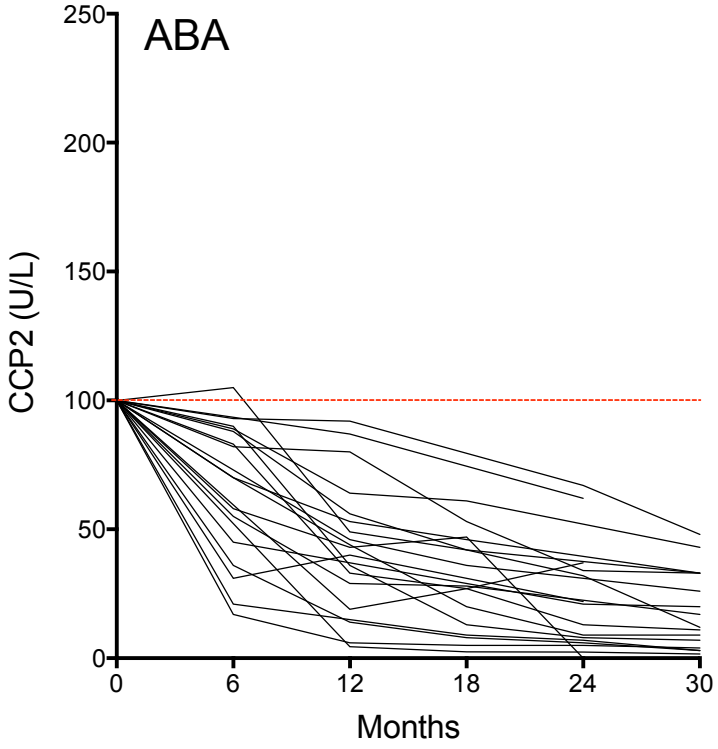


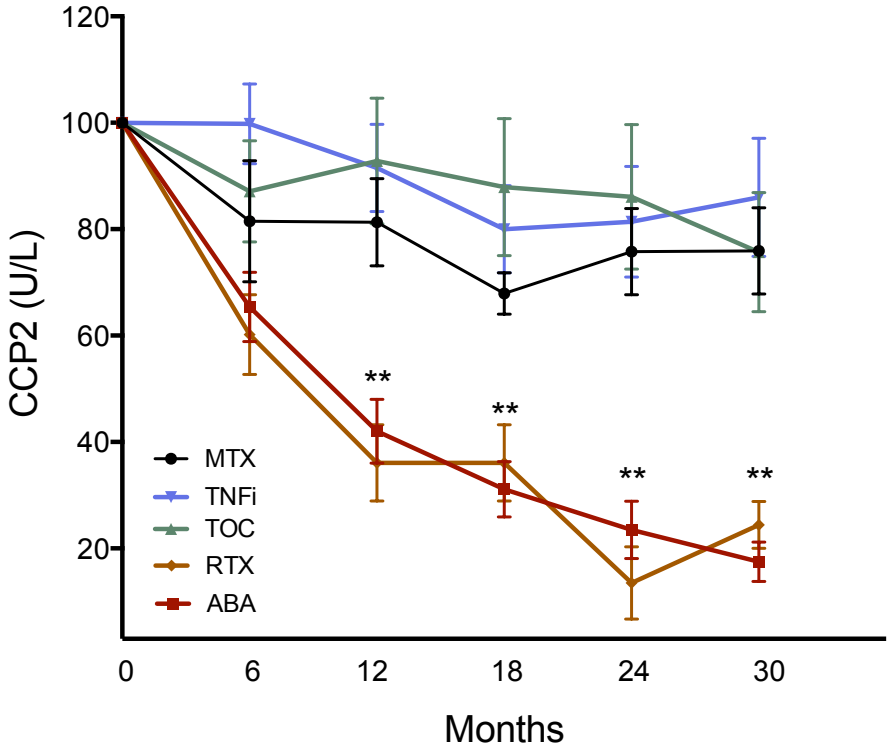


Individual Patients

Group

Effect of abatacept treatment

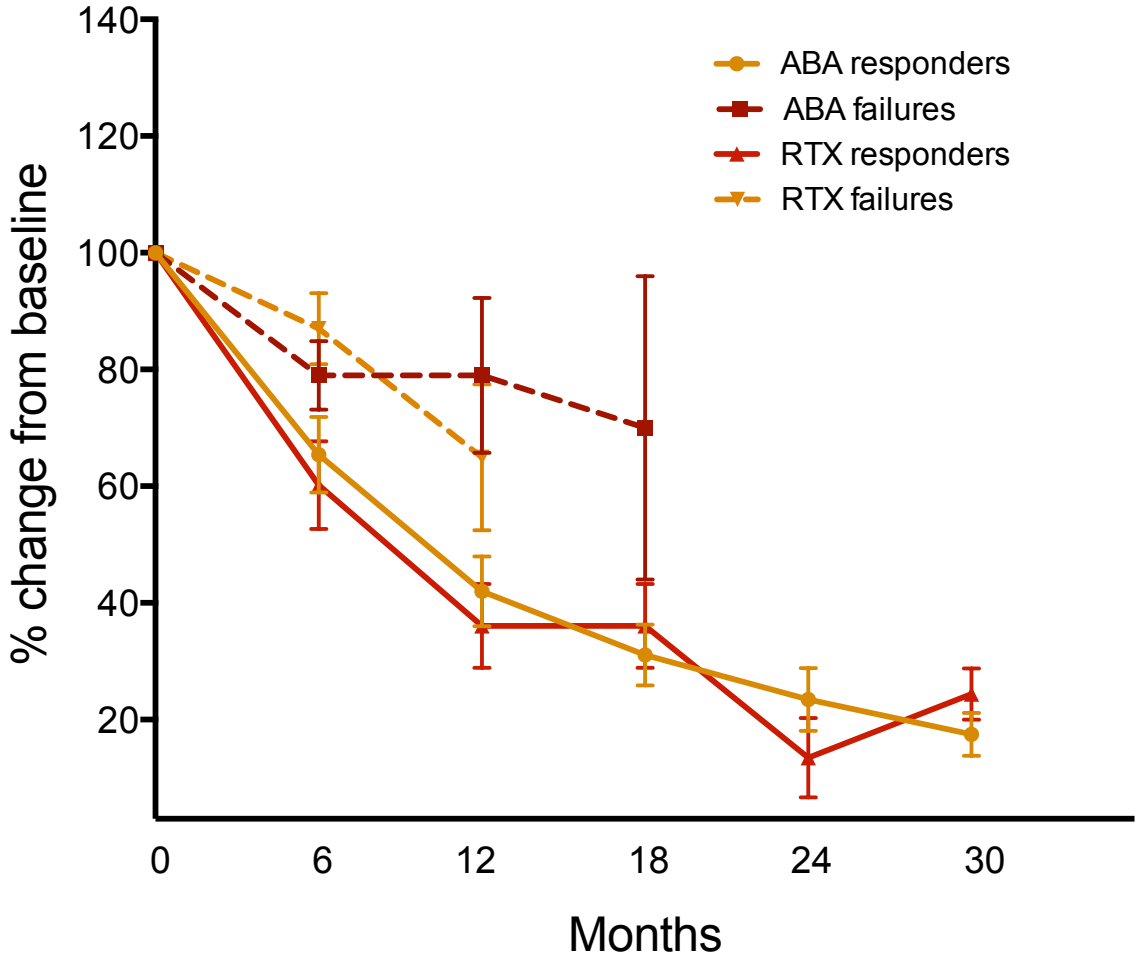




Individual Patients

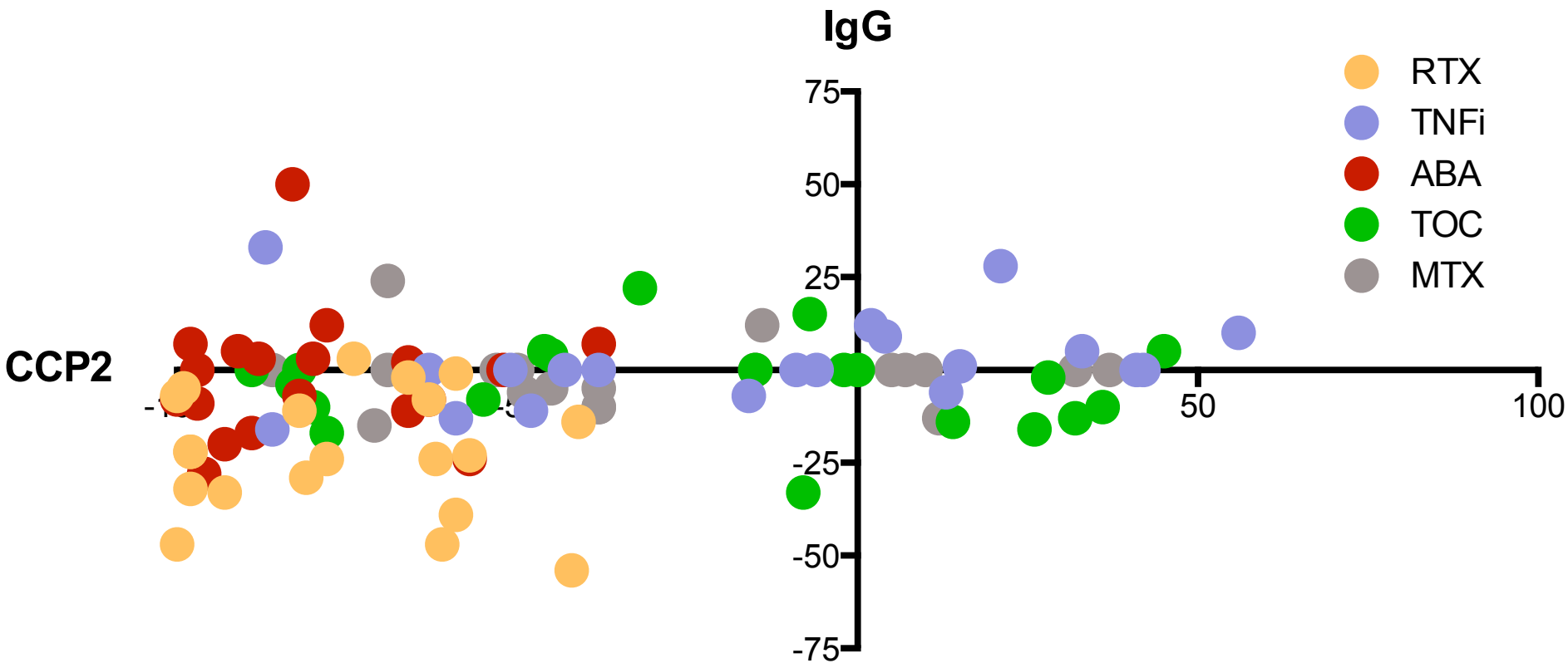
Group

Comparison of abatacept/rituximab responders and non-responders



Wunderlich et al., Sem Arth Rheum 2016, in press

Comparison of the effect on CCP2 and IgG levels of the 5 different treatment modalities



Wunderlich et al., Sem Arth Rheum 2016, in press

Conclusions

1. Anti-modified protein antibody (AMPA) response in RA
2. ACPA and RF induce local and systemic bone loss
3. ACPA and AMPA responses determine disease chronicity
4. Individual DMARDs differ in their effects on ACPA