

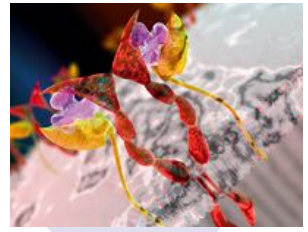
Immunogenicity and response to biologics



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Inserm U844
IRMB

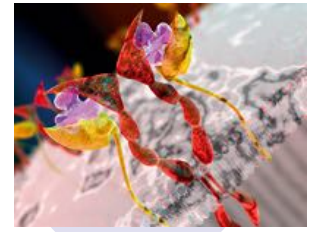
Unmet needs in RA immunotherapy



- ⇒ Select subgroup of patients with bad prognosis to be treated early with biologics
- ⇒ Improve tolerance & efficacy of biologics (Cure?)
- ⇒ Identify selective responders to TNF α , IL6R, IL17 blockade
- ⇒ When to stop therapy
- ⇒ Long term cost and medico-economical evaluation
- ⇒ **biomarkers!**

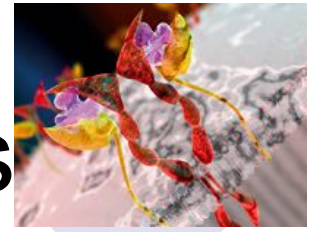


The Next Great Advances in RA Care



- ▶ New Drugs available: Rituximab, Abatacept, Tocilizumab, Golimumab...
- ▶ Advances in bone protection
- ▶ Advances in imaging
- ▶ Personalized medicine (biomarkers, proteomics) ?
- ▶ Smarter use of existing therapies
- ▶ Metric guided treatment protocols

Biotherapies in RA: biomarkers



Disease biomarkers

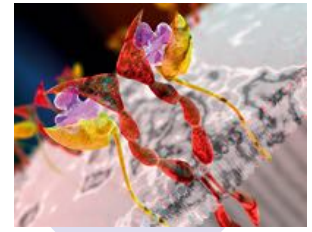
Early
diagnostic
Prognosis
Monitoring/
Recurrence

Pharmacological markers

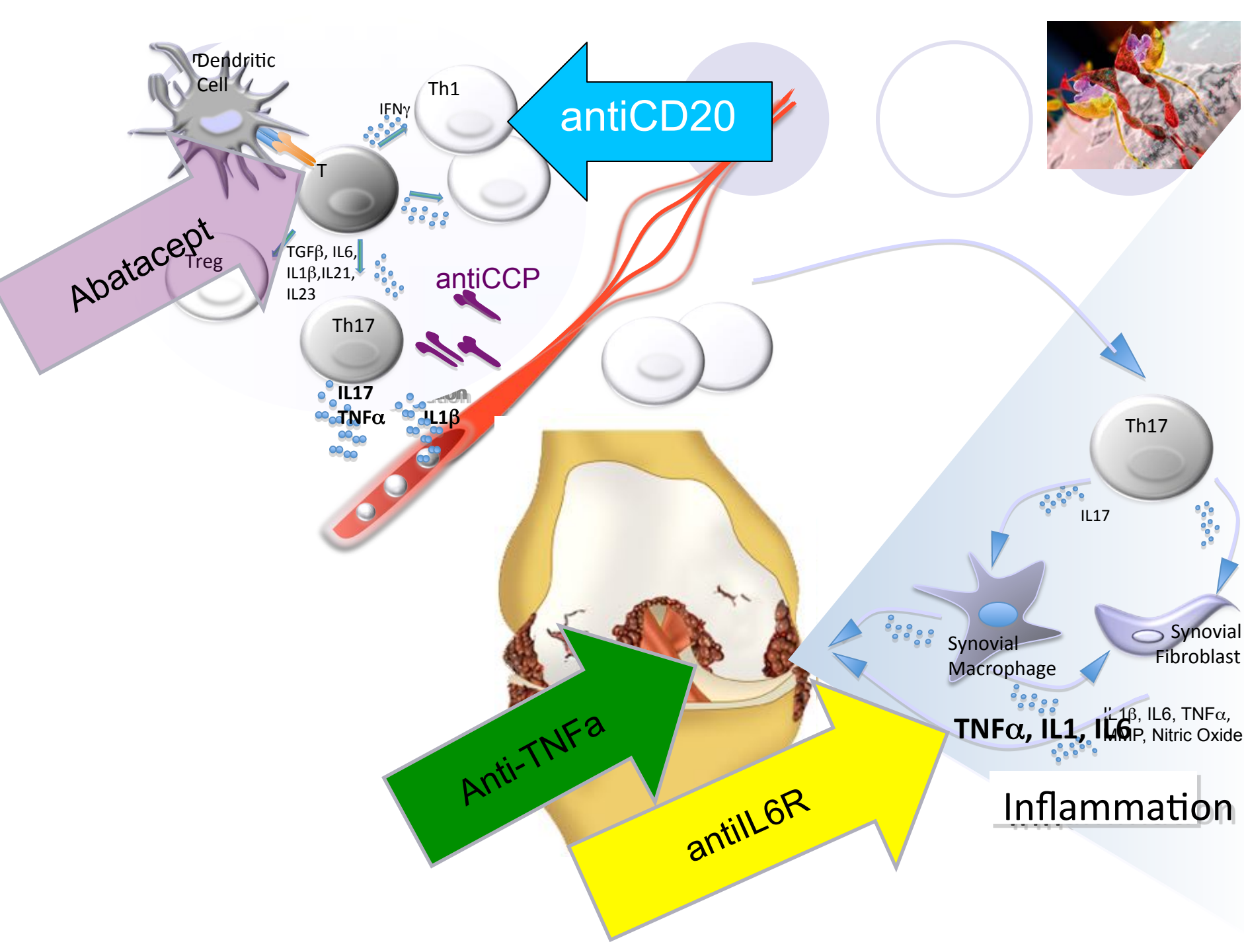
Optimize biologics delivery
PK markers
AAB

Predictive
Pharmacodiagnosics
identify the responders
Select the biologics

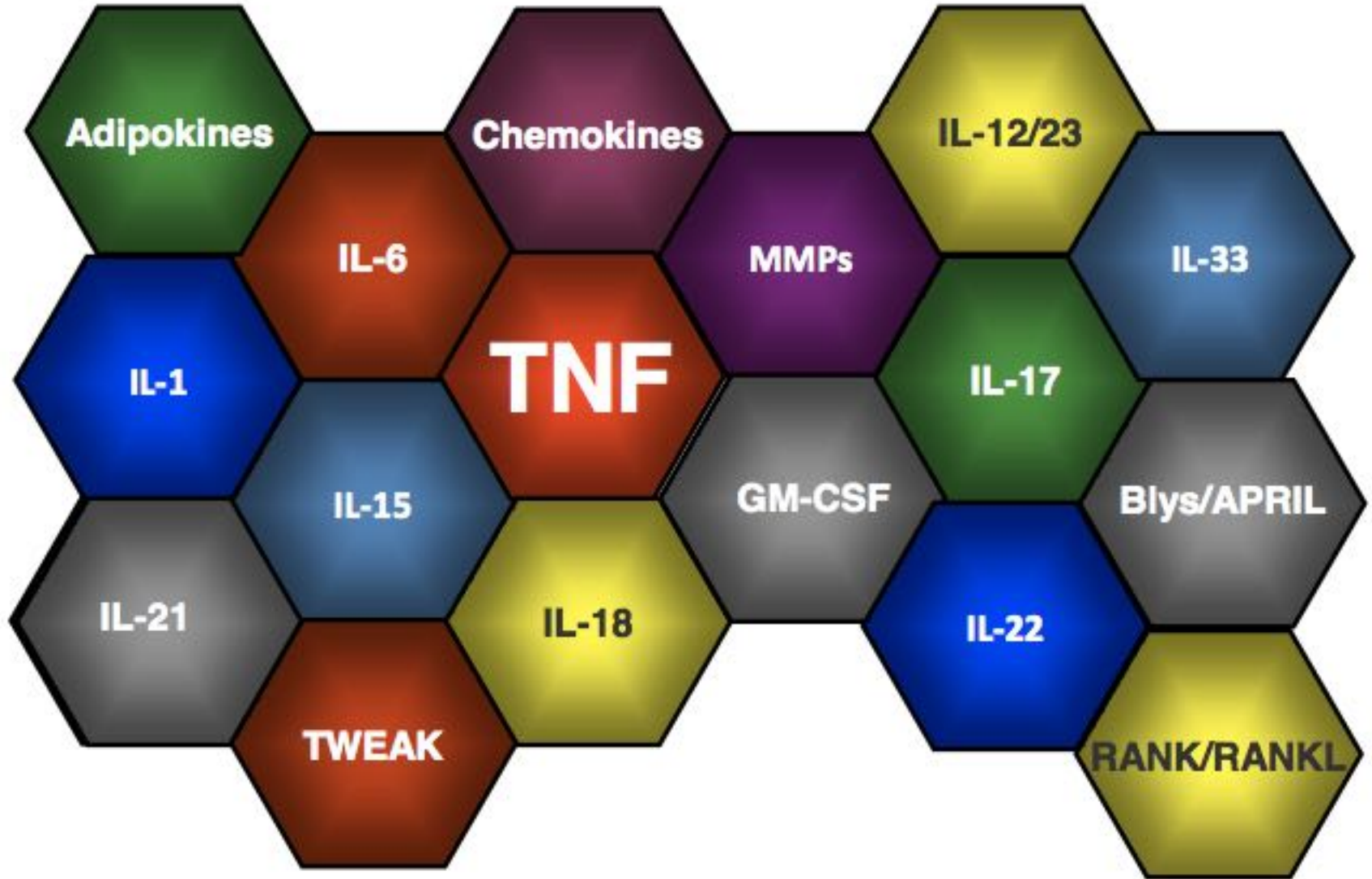
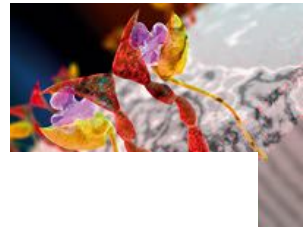
Objective: optimize the use of biologics in RA



- Pharmacological markers:
 - Identify antibody against biologics (AAB)
 - Association with biologics concentration
- Correlation with SAE
- Associated with clinical response/relapse
- Can we decrease AAB with concomitant DMARDS?



Targeting cytokines



Targeting the immune response in RA



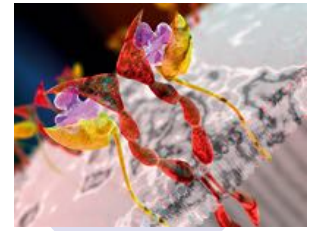
Cytokines
IL1b
TNFa
IL6
IL17A

antiTNFa:
Enbrel
Humira
Remicade
Simponi
Cimzia
antiIL6R:
Tocilizumab,
antiIL17

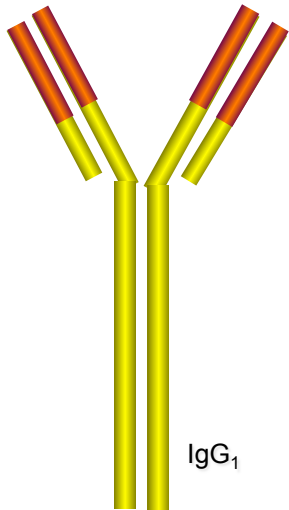
Lymphocytes B/Th1/Th17
Monocytes M1

Anti-CD20:
Rituximab
Ocrelizumab
CTLA4Ig:
abatacept
Anti-p40:
Ustekinumab

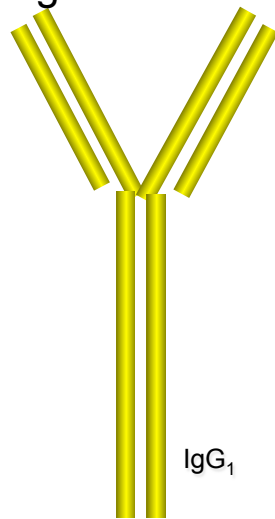
Anti-TNF α biologics



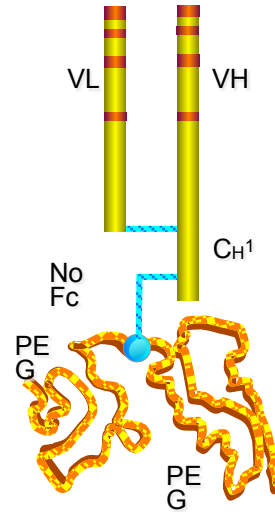
Infliximab



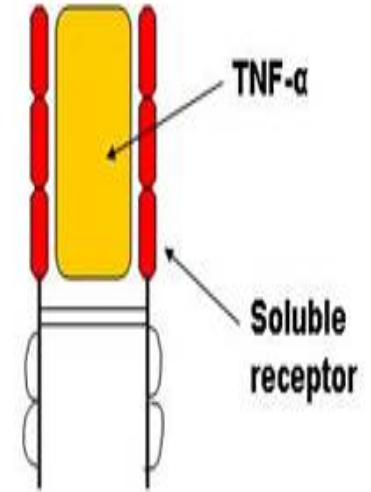
Adalimumab
golimumab



Certolizumab Pegol



etanercept



Receptor analog

Chimeric monoclonal antibody (75% human IgG₁ isotype)

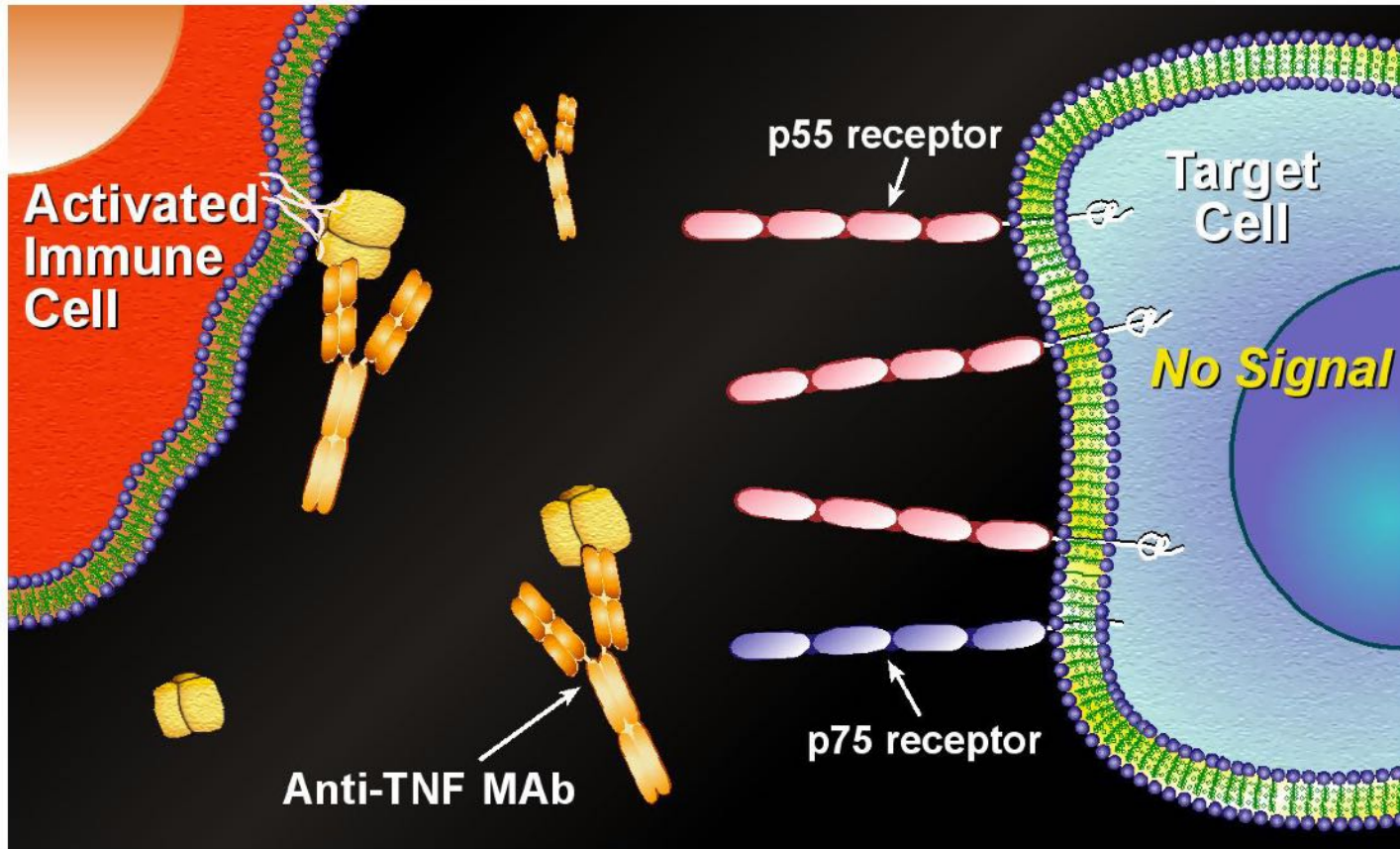
Human recombinant antibody (100% human IgG₁ isotype)

Humanized Fab' fragment (95% human IgG₁ isotype)

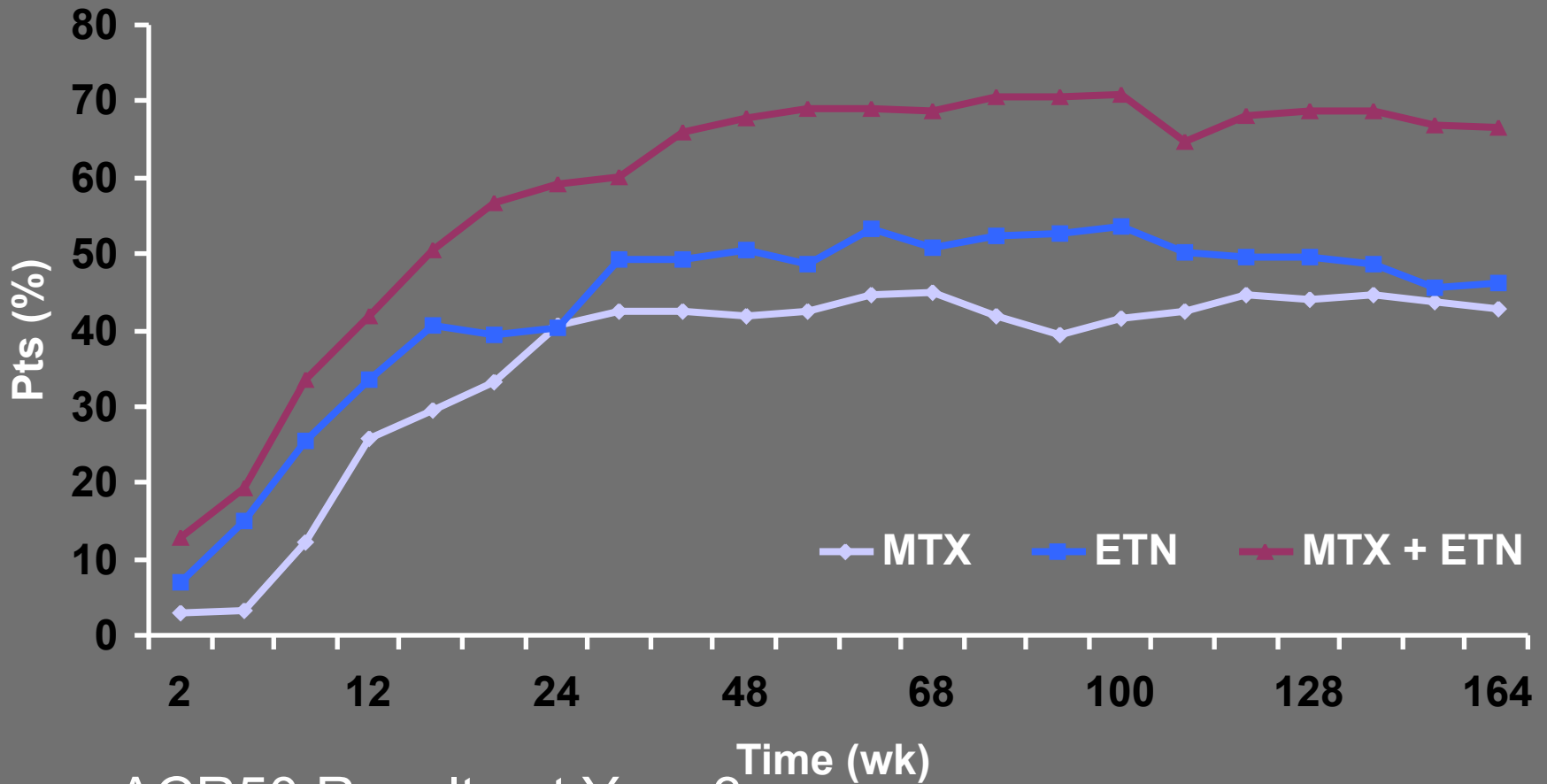
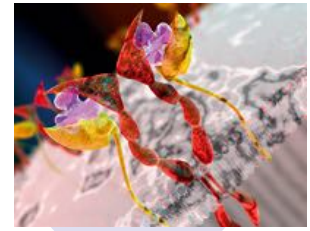
■ Mouse
■ Human

PEG, polyethylene glycol.

TNF Inhibition: Monoclonal Antibodies

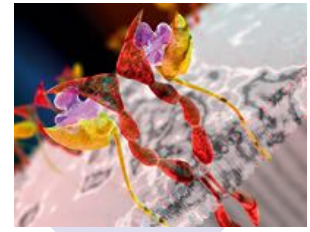


Efficiency of anti TNFalpha



ACR50 Results at Year 3

Efficacy of antiTNFa in RA



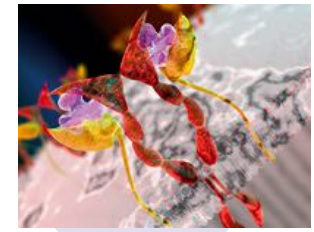
- ✓ Similar effects of infliximab, etanercept, adalimumab, golimumab with approx 70% response rate (DAS28, EULAR, ACR20).
- ✓ Prevent structural damage +++

BUT:

- ✓ < 20% remission
- ✓ Flare when biologics withdrawn
- ✓ Side effects



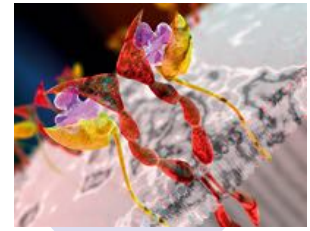
All anti-TNFs are immunogenic & AAB present in all IMID



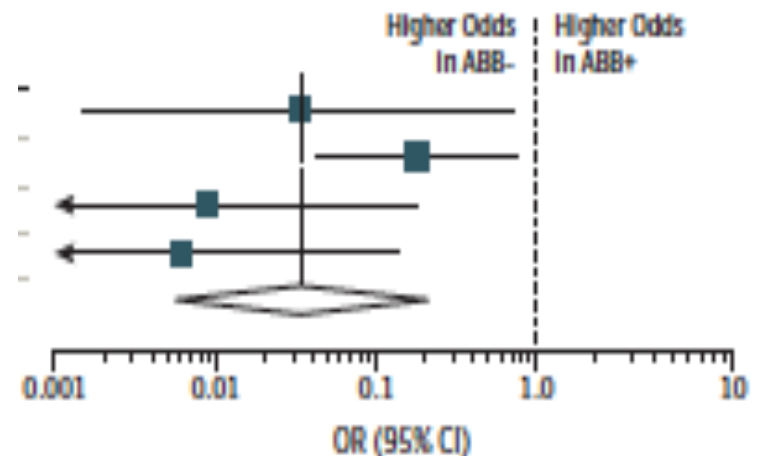
| | | Patients, % | | | |
|---------------------------|-------------------------|----------------------|--------|-----------------------|--------|
| | | Episodic Maintenance | | Scheduled Maintenance | |
| | | DMARD- | DMARD+ | DMARD- | DMARD+ |
| Infliximab ¹ | (CD 5 mg/kg) | 38% | 16% | 11% | 7% |
| | (CD 10 mg/kg) | | | 8% | 4% |
| Infliximab ² | (UC 5 mg/kg) | No data | | 19% | 2% |
| | (UC 10 mg/kg) | | | 9% | 4% |
| Certolizumab ³ | (PRECiSE I) | | | 10% | 4% |
| Certolizumab ⁴ | (PRECiSE II) | 24% | 8% | 12% | 2% |
| Adalimumab ⁵ | (RA, all doses) | No data | | 28% | 8% |
| | Adalimumab ⁶ | | | (CLASSIC II) | 3.8% |

1. Hanauer SB et al. *Clin Gastroenterol Hepatol.* 2004;2:542-553; 2. Sandborn WJ et al. DDW 2007 Poster and abstract T1273; 3. Sandborn WJ et al. *N Engl J Med.* 2007;357:228-238; 4. Schreiber S et al. *N Engl J Med.* 2007;357:239-250; 5. Sandborn WJ et al. *Gut.* 2007;56:1232-1239. 6. Sandborn WJ et al. *JAMA.* April 13, 2011—Vol 305, No. 14

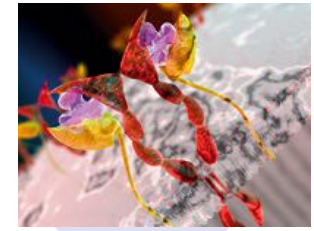
AAB increase therapeutic failure independently of IMID



- In RA, AAB positivity associated with less than 3% EULAR response
- In AS, ASAS response rate decrease to 28% in AAB+
- In IBD, AAB positive patients have 47% chance of achieving clinical response
- In RA, psoriasis and IBD, AAB+ is associated with loss of response month 6 (RR=3)



AAB reduced therapeutic response of antiTNFa in IMID

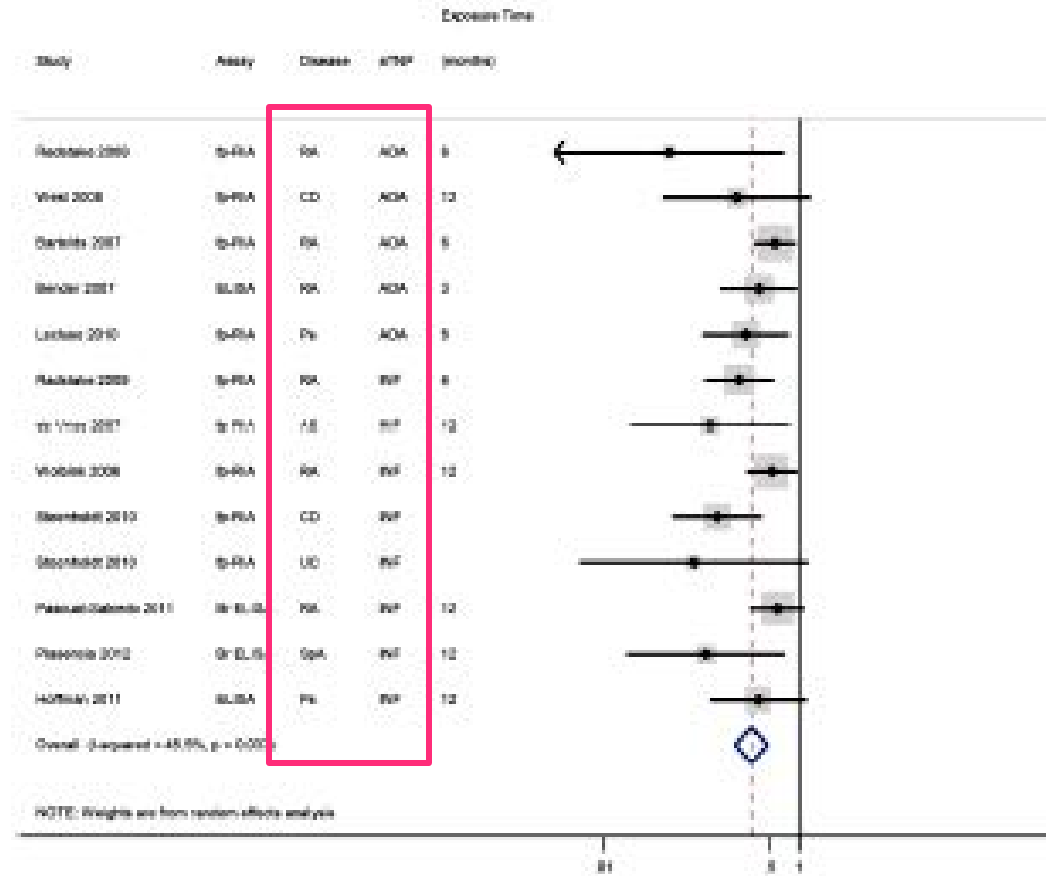


- In a meta-analysis of 17 studies, (865 patients), AAB to infliximab or adalimumab reduces drug response rate of 68%

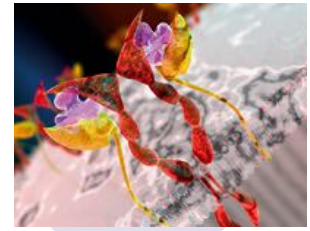
- Independent of IMID type

- RIA more sensitive than ELISA

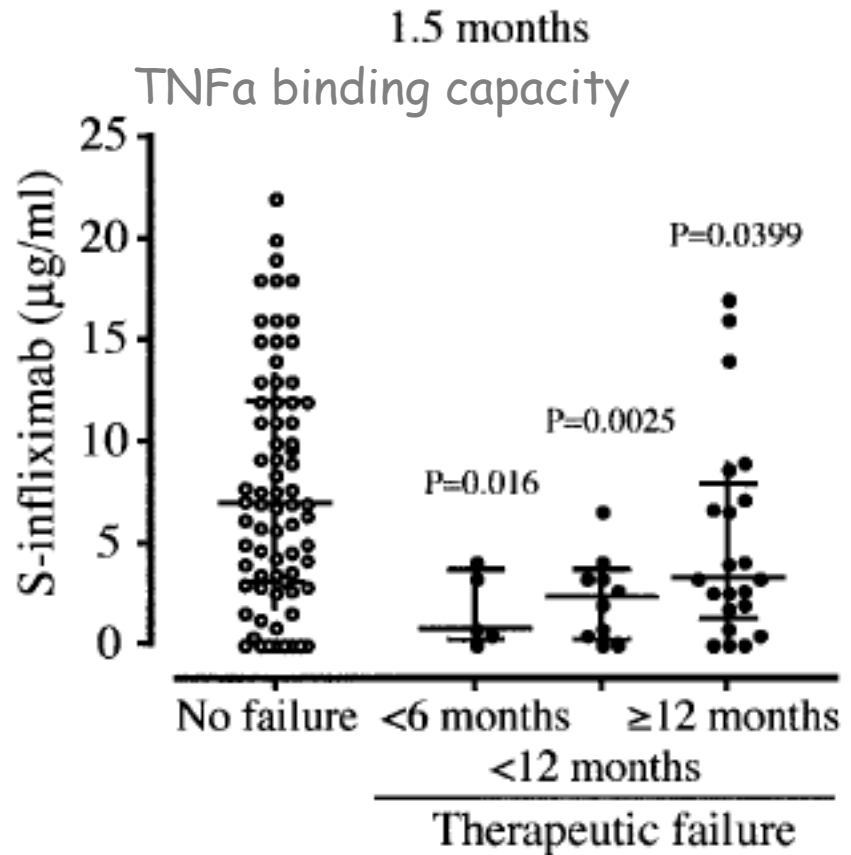
- No AAB in etanercept



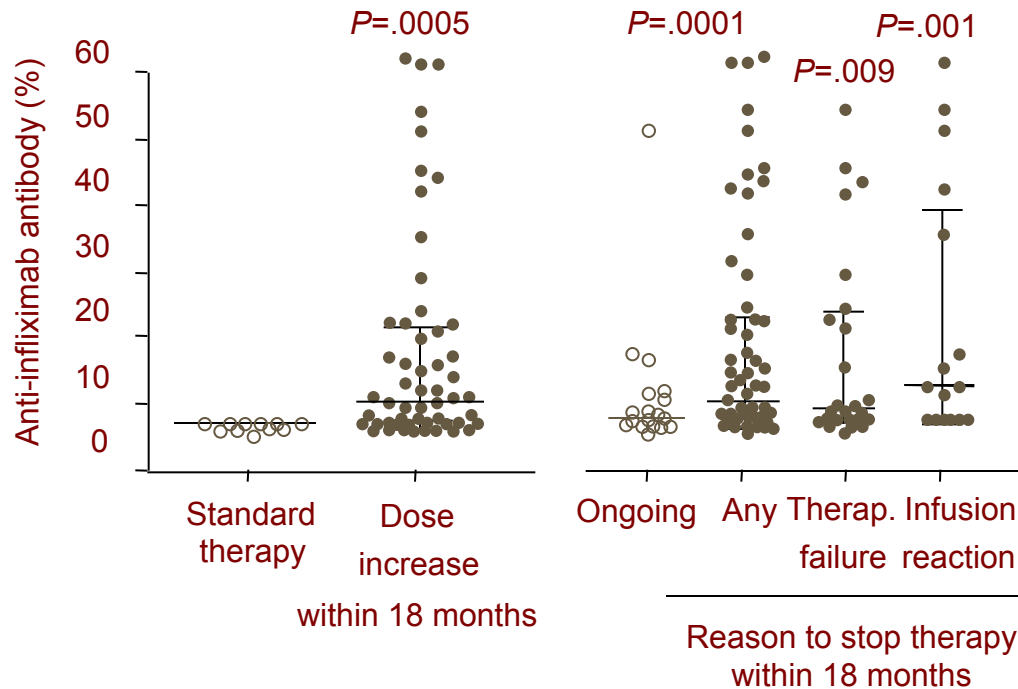
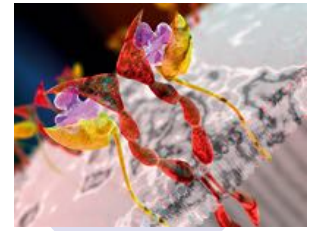
Low infliximab bioavailability predicts treatment failure



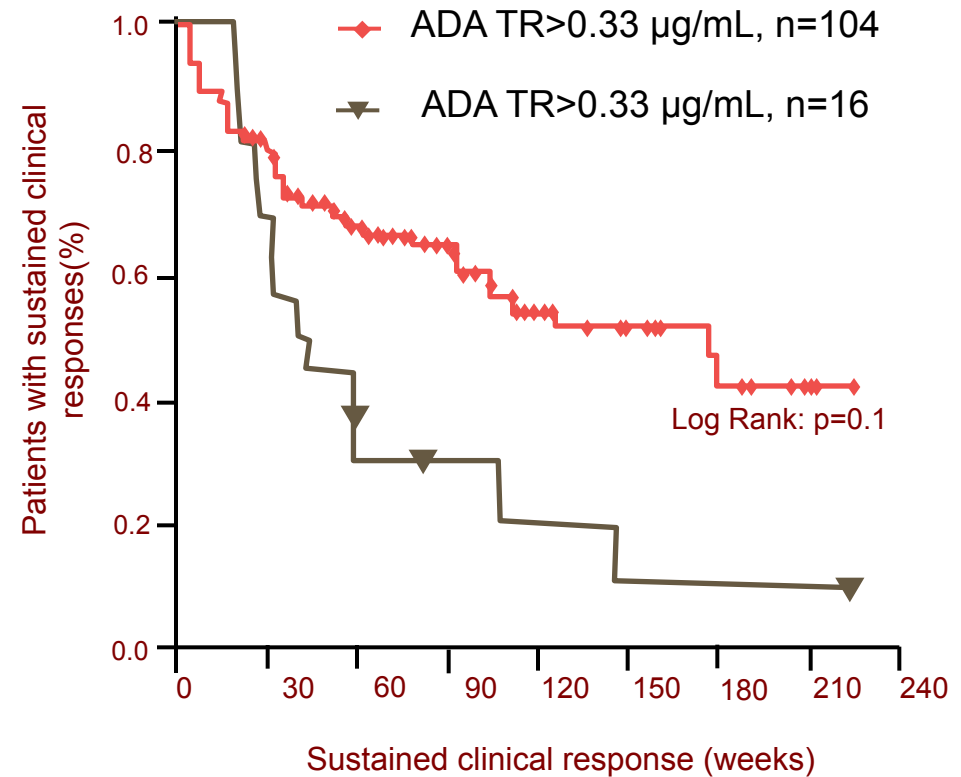
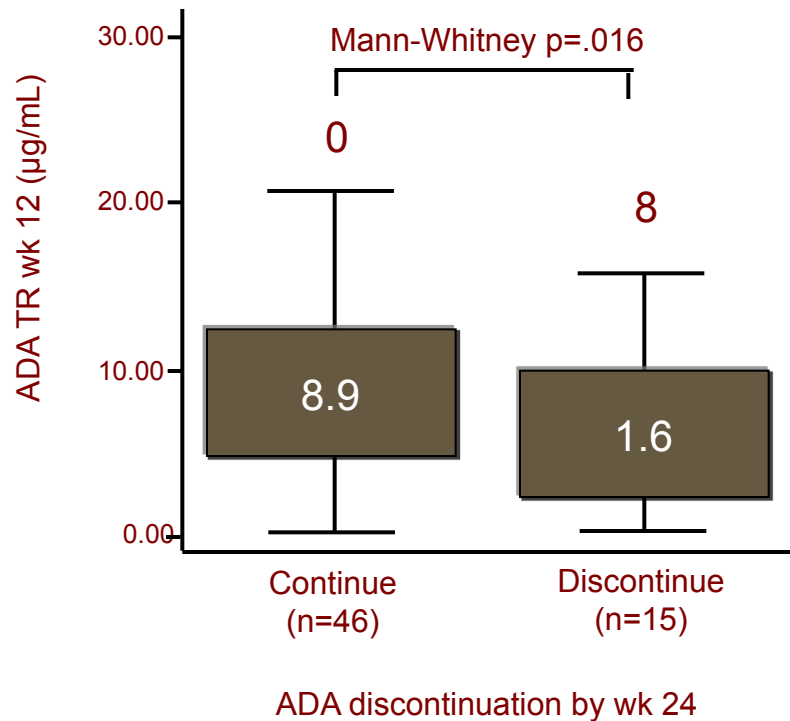
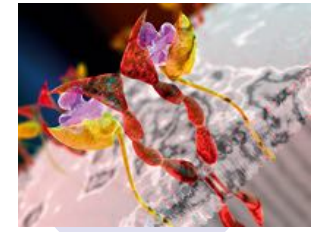
- Bioavailability of infliximab before the third infusion is highly variable.
- Low tumor necrosis factor binding capacity due to infliximab in sera day 45 predicts response
- High baseline disease activity (DAS28) was associated with low levels of infliximab and later development of AAB



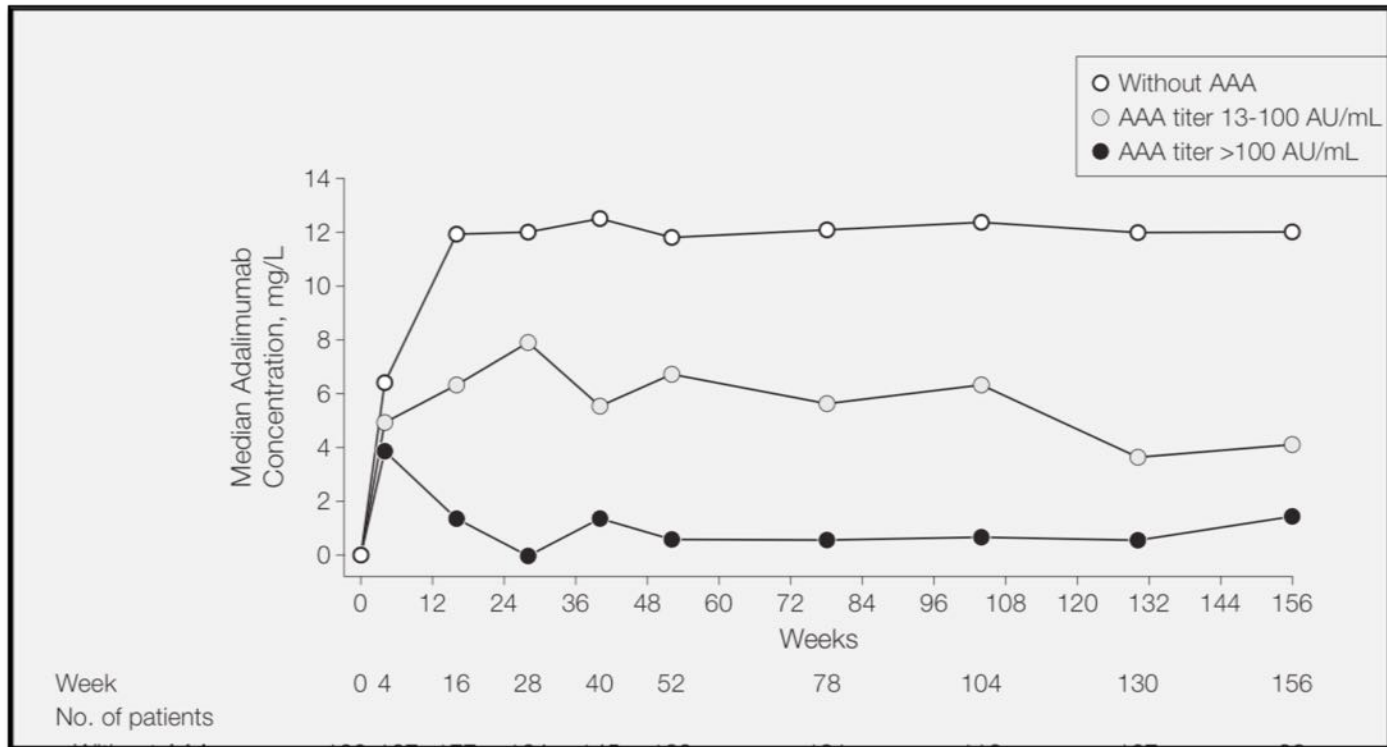
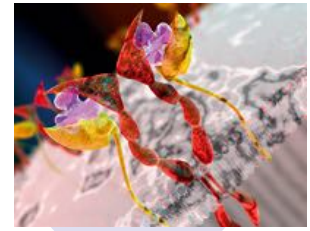
HACA to infliximab increase therapeutic failure and infusion reaction in RA



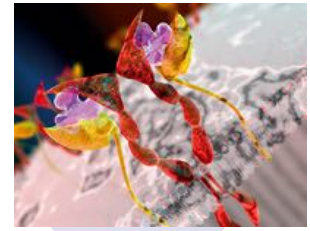
Adalimumab concentration Predict long-term Response in IBD



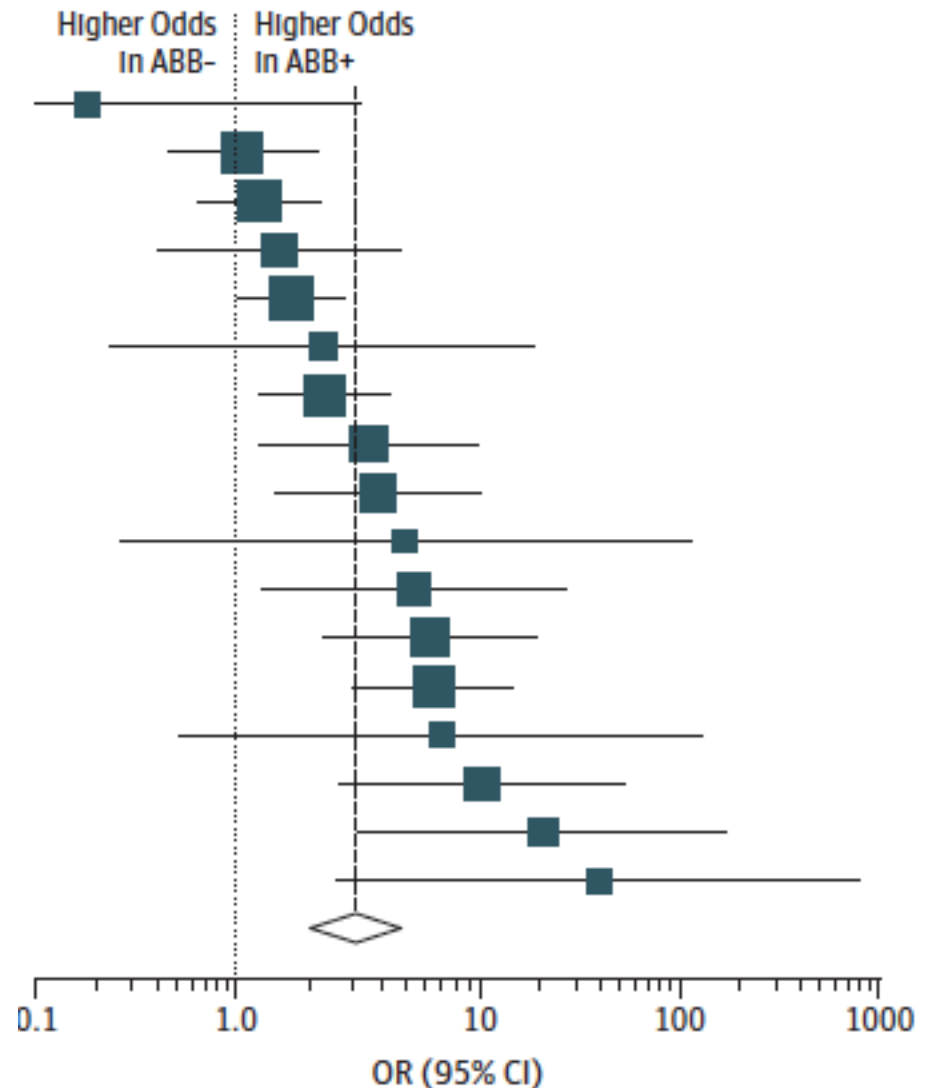
AAB decrease HUMIRA concentration.



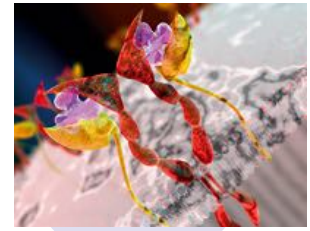
AAB are associated with hypersensitivity response in IMiD



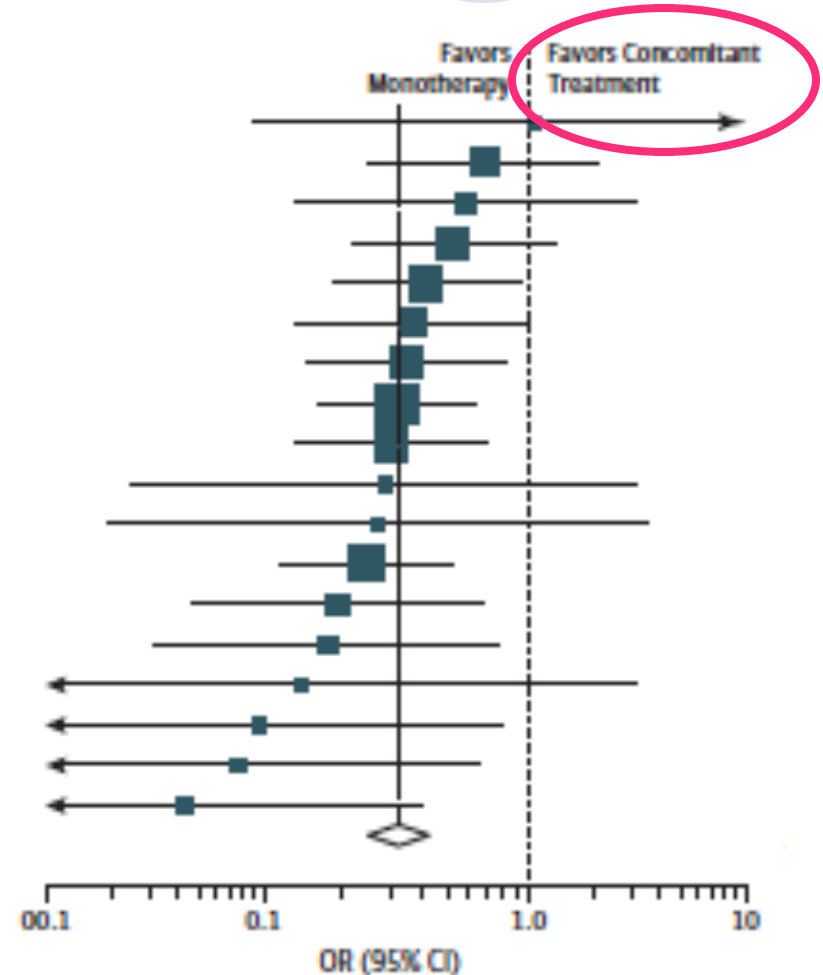
- Side effects related to AAB was increased (RR=3.97) for RA, IBD and AS
- AAB+ patients discontinued antiTNFa more frequently (OR=3.53)

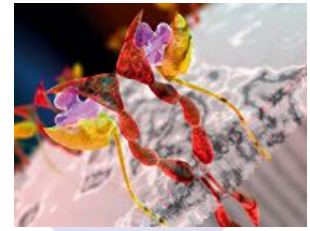
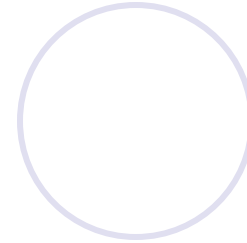
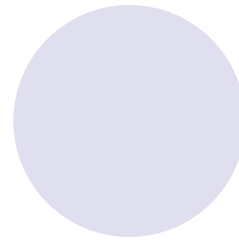
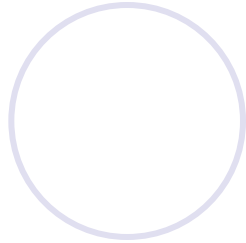
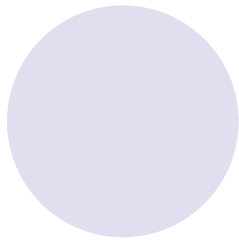


AAB decreased with combined DMARD



- DMARD reduced risk of AAB of 68%
- MTX (7.5-25mg/week) was most commonly associated with RA, reduced AAB of 69%
- MTX reduced risk of AAB of 48% in AS
- AZA (2-2.5mg/Kg/day) reduced risk of AAB of 42%
- No effect of cortisone





- AAB is frequent in IMiD treated with antiTNFa (11-28%)
- Associated with significant loss of clinical response
- Associated with decreased drug concentration
- Associated with hypersensitivity
- Can be reduced by combined DMARD (MTX, AZA)

Targeting the immune response in RA

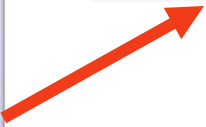


Cytokines
IL1b
TNFa
IL6
IL17A

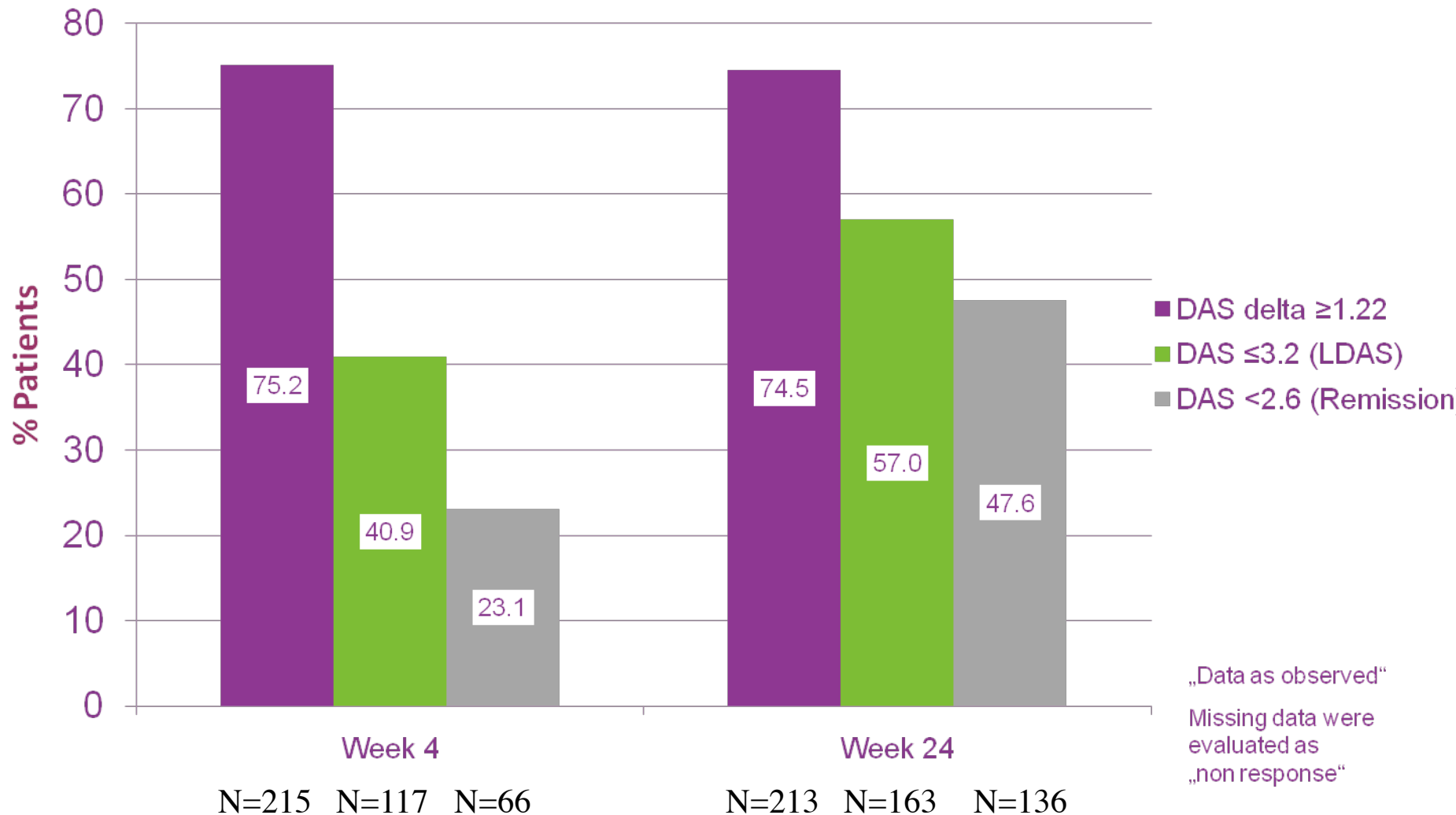
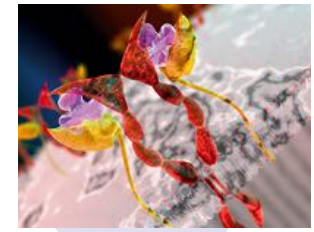
antiTNFa:
Enbrel
Humira
Remicade
antiIL6R:
Tocilizumab,
antiIL17

Lymphocytes B/Th1/Th17
Monocytes M1

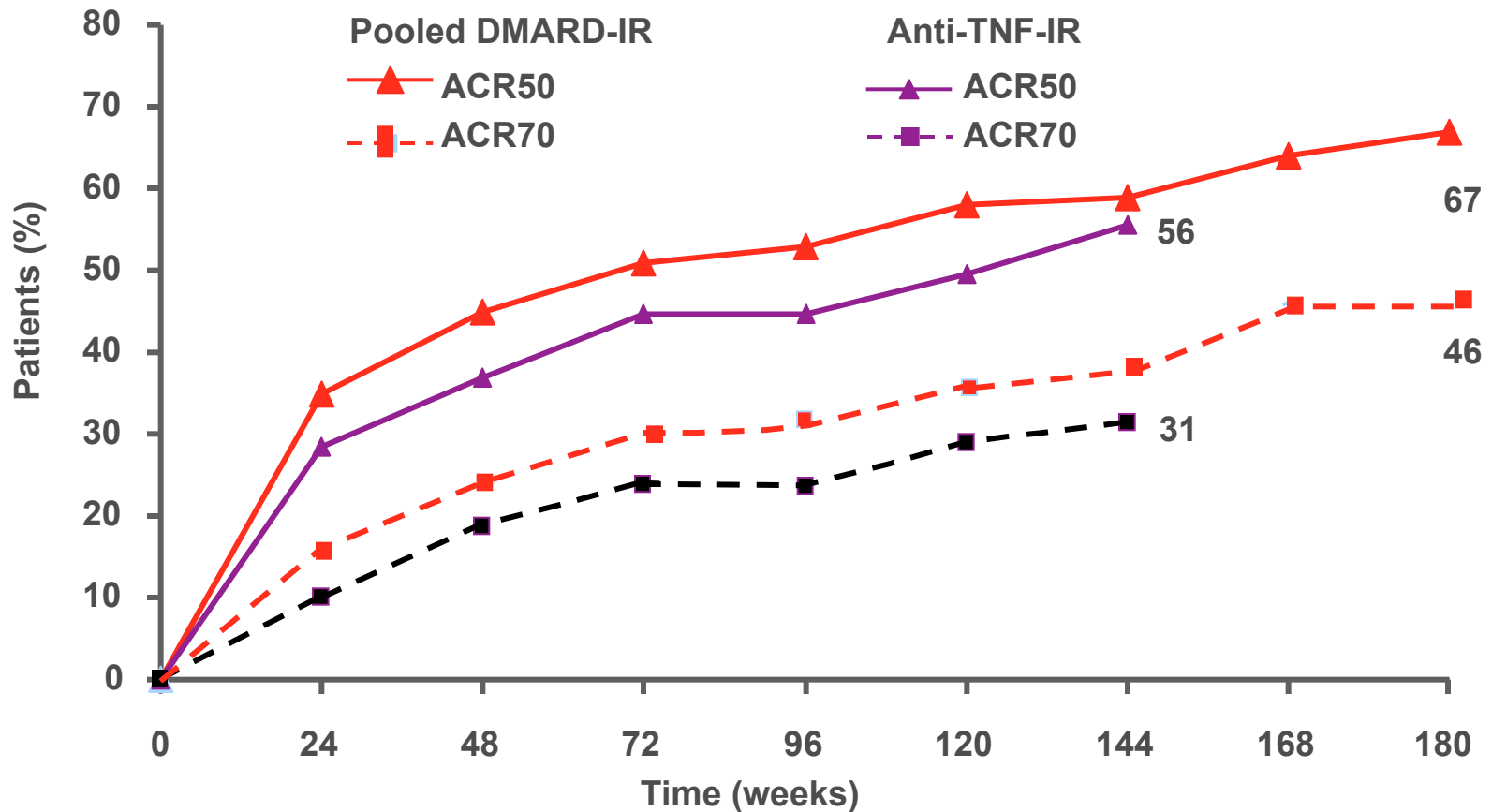
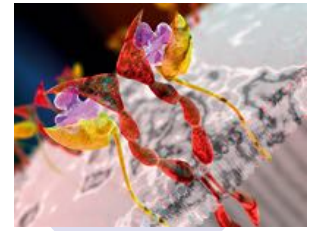
Anti-CD20:
Rituximab
Ocrelizumab
CTLA4Ig:
abatacept
Anti-p40:
Ustekinumab



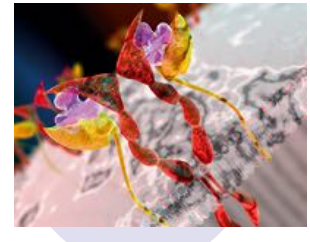
Efficiency of targeting IL6: Tocilizumab in RA



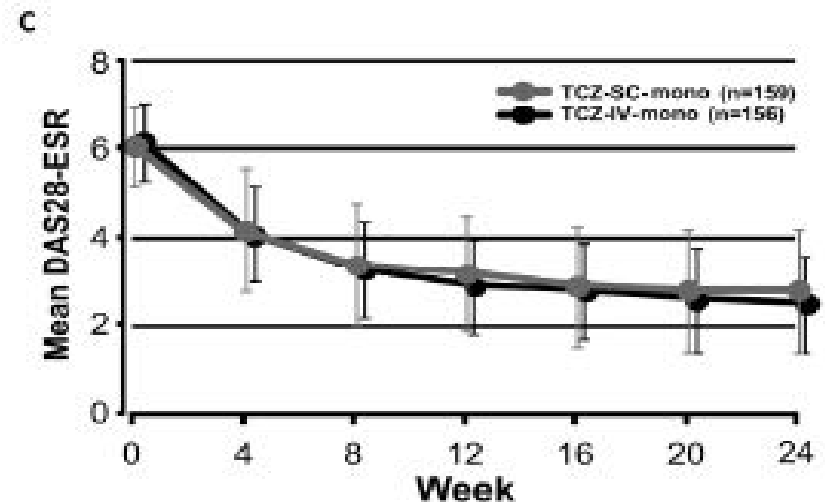
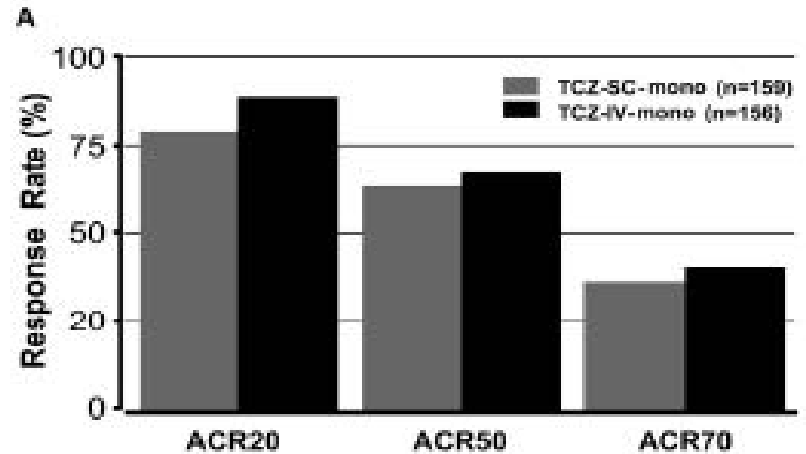
Efficiency of targeting IL6: Tocilizumab in RA: Efficacy at 3.5 years



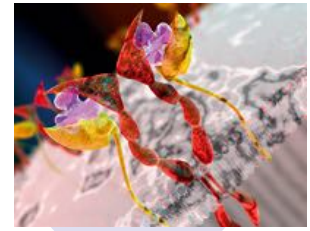
Hypersensitivity of TCZ



- incidence of SIRs from SC injection was 3.5%
- incidence of IV IRRs was 6.9% (12/173 of patients).
- One patient had an anaphylactic reaction after the second infusion (0.6%).
- No patients in the TCZ-SC group experienced serious hypersensitivity.

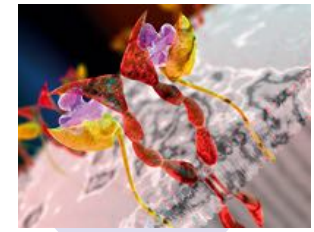


Immunogenicity to TCZ



- 4199 RA patients followed in 5 core studies
- Hypersensitivity reactions, primarily reflected by events of urticaria/rash following infusion, were reported in 46 patients (1%) treated with TCZ 8 mg/kg
- cutaneous local reaction (3.5%)
- 8 anaphylatic reactions

Immunogenicity to TCZ



| Variable | Anaphylactic Reaction (n = 9*) | Infusion-Related/ Hypersensitivity Reaction (n = 6) | Other Events (n = 6) | All Events (N = 21) |
|---|-----------------------------------|---|-------------------------|------------------------|
| Patients providing samples for screening/ confirmation assays | 8 (88.9) | 6 (100) | 5 (83.3) | 19 (90.5) |
| Patients with samples that tested positive on screening/confirmation assays | 5 (55.6) | 2 (33.3) | 1 (16.7) | 8 (38.1) |
| Patients with samples that tested negative on screening/confirmation assay, but tested positive on SPR or IgE assay | 0 | 1 (16.7) | 0 | 1 (4.8) |

SPR = surface plasmon resonance; IgE = immunoglobulin E.

- 2.3% TCZ treated RA developed AAB (ELISA)
- of 14 RA with hypersensitivity events, 50% were AAB+

Targeting the immune response in RA



Cytokines
IL1b
TNFa
IL6
IL17A

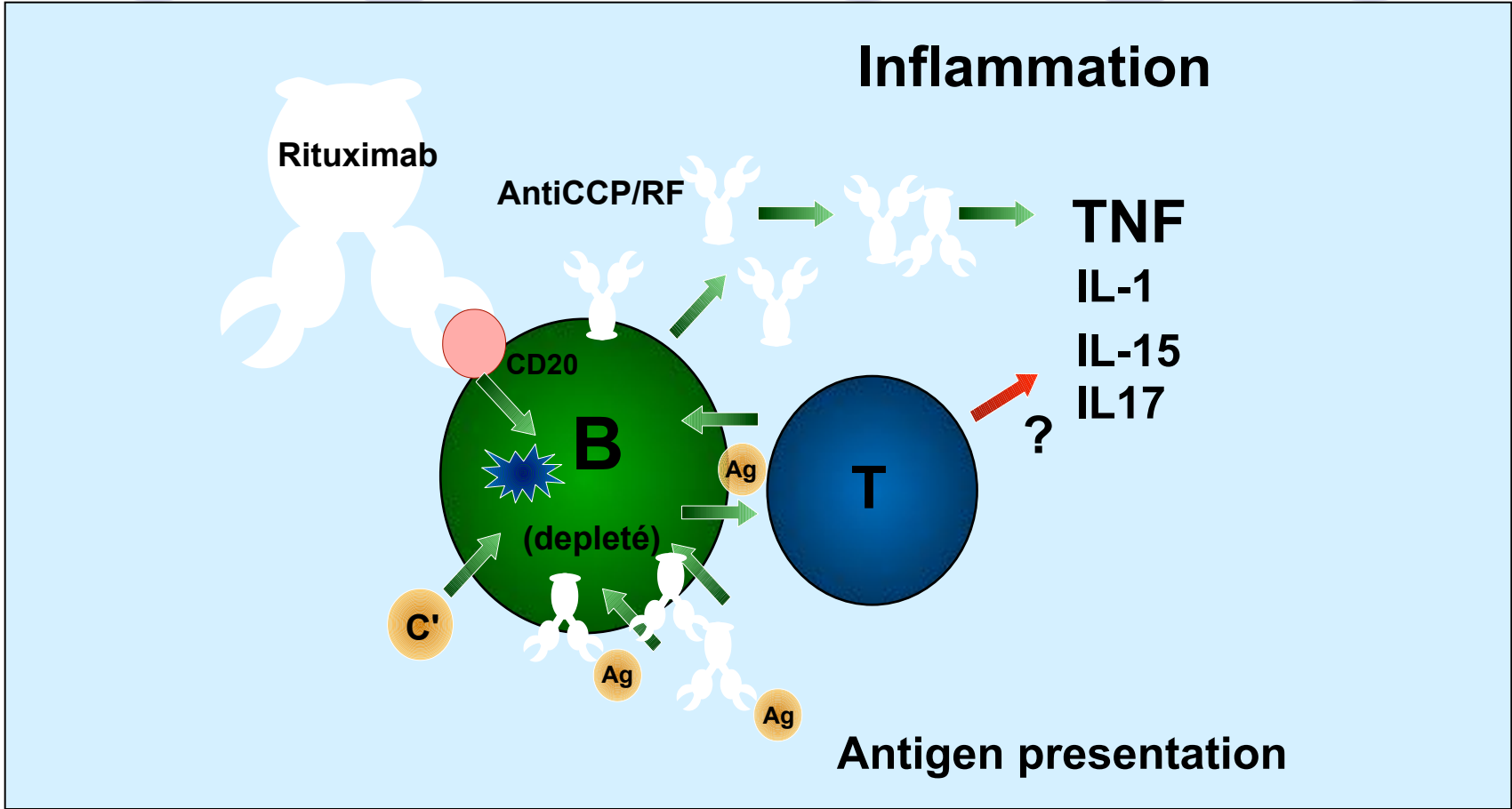
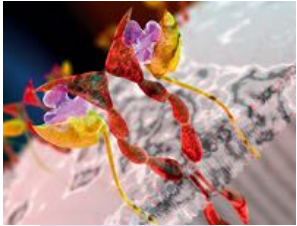
antiTNFa:
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Lymphocytes B/Th1/Th17
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Anti-CD20:
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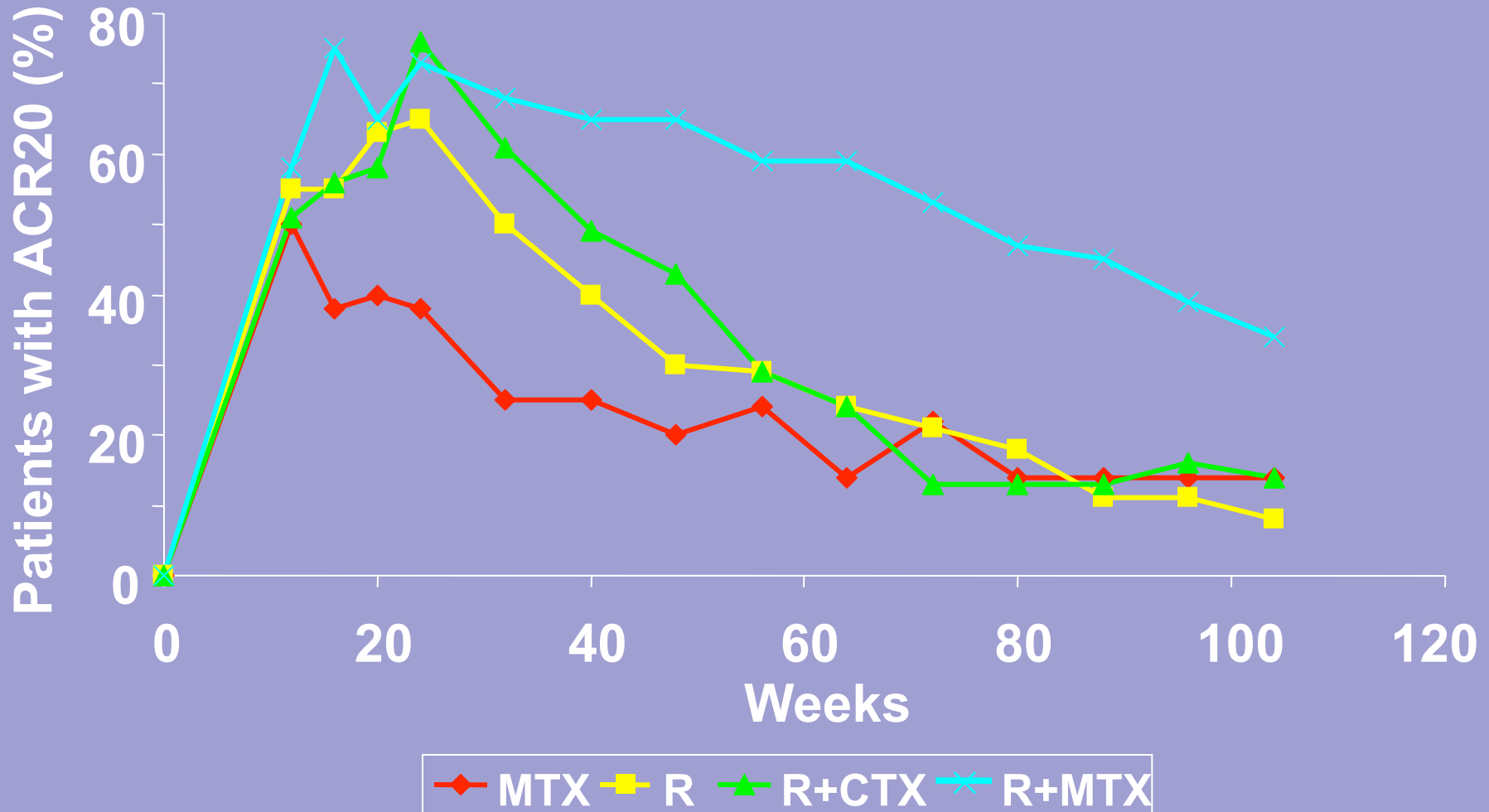
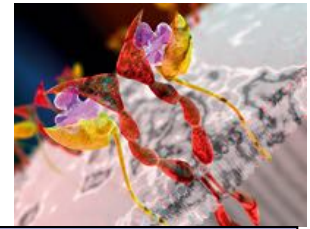


B cell targeted therapy: rituximab

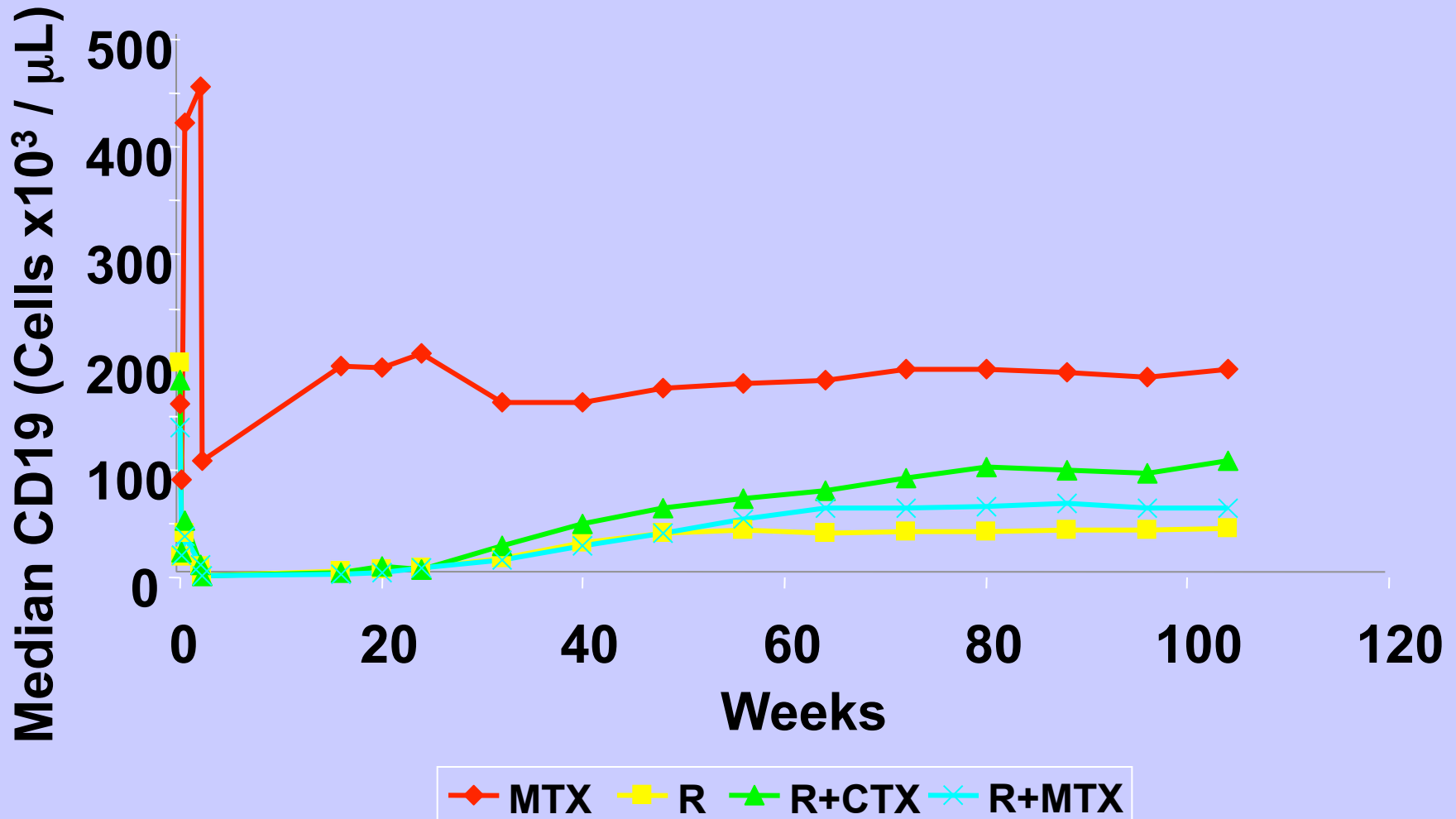
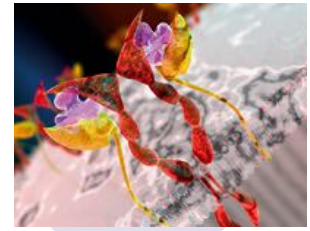


Impact on B cell functions: cytokine release, AG presentation, T cell helper, Ab release

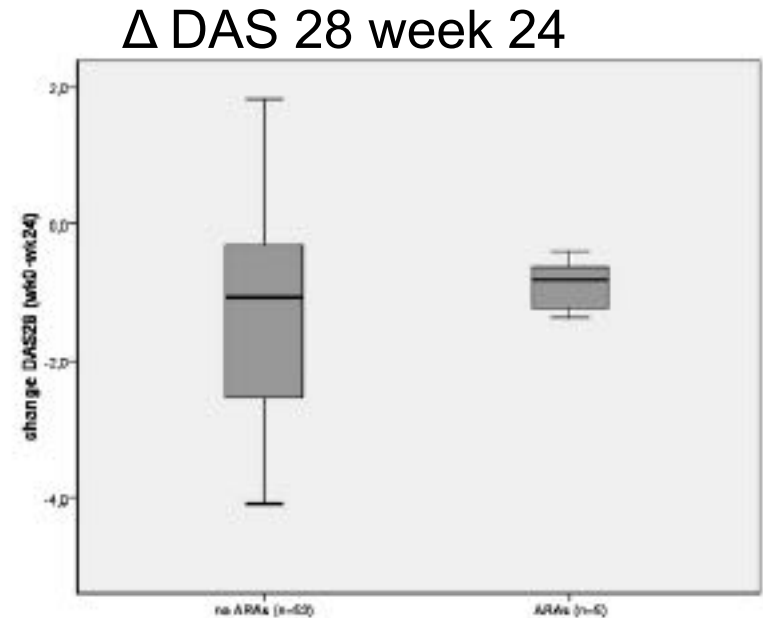
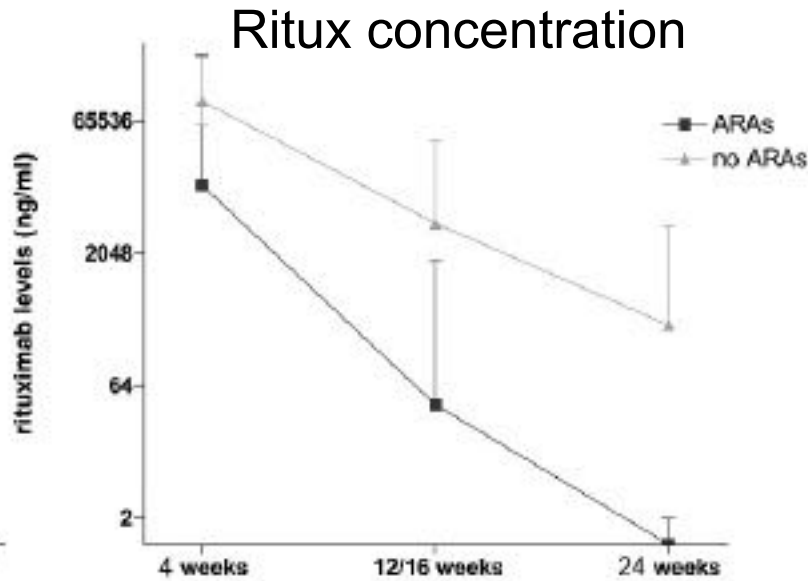
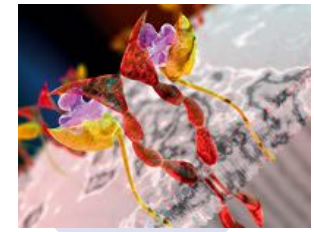
Targeting B cells with Rituximab : ACR Responses over 2 Years



Blood B cells over 2 Years

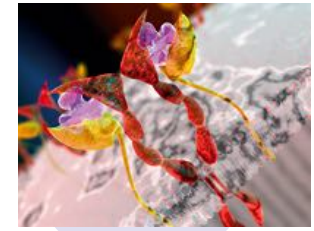


Immunogenicity of Rituximab



- 5/58 RA patients developed AAB (8.6%)
- AAB decreased levels of Ritux concentration
- However, AAB+ did not impact on B cell depletion or on clinical response at week 24.

Immunogenicity of Rituximab

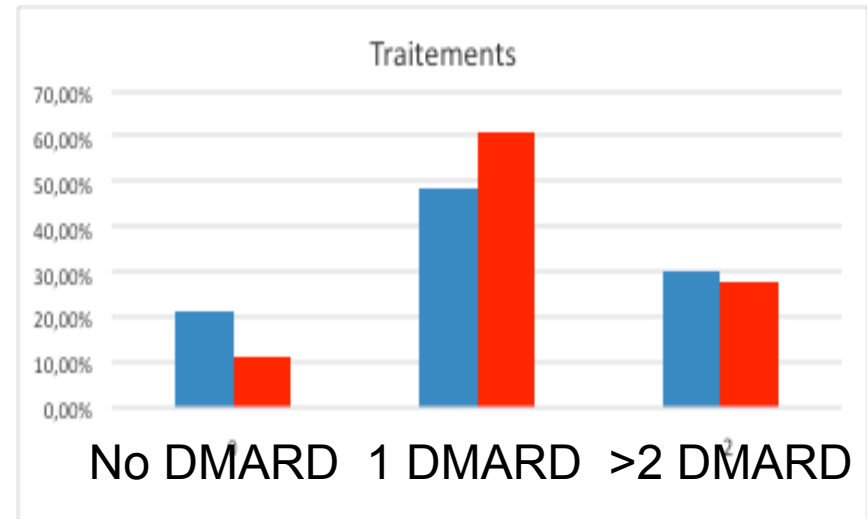


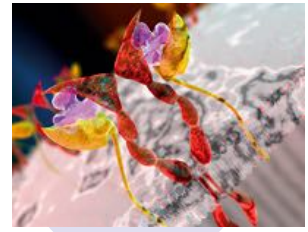
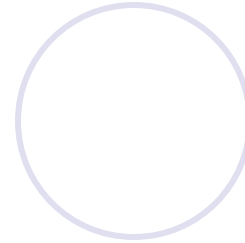
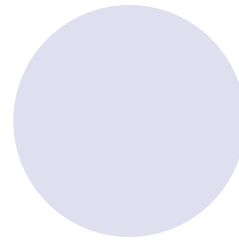
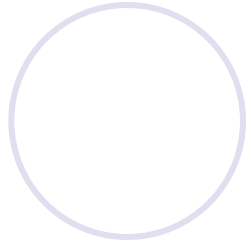
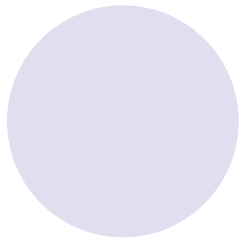
| | Placebo | RTX 2 x 500 mg | RTX 2 x 1 000 mg |
|---------------------|--------------|-------------------|---------------------|
| AAB+ week 24 | 0.7 % | 4.2 % | 2.7 % |

Emery P et al. Arthr & Rheum 2006;54(5):1390-400.

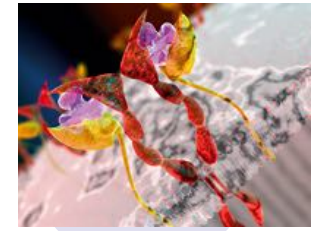
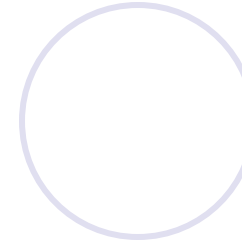
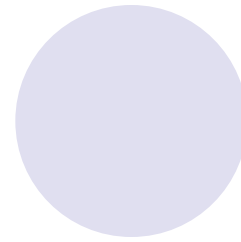
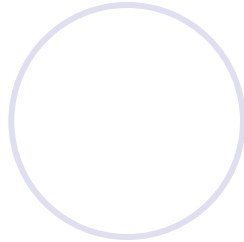
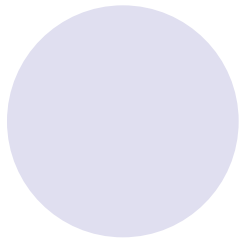
10 patients developed AAB+

- No correlation with hypersensitivity response
- No SAE in AAB+ patients
- ACR 20 response week 24 obtained in 6/10 AAB + patients
- Combined therapy did not improve response (n=155)





- 2.3% TCZ treated RA developed AAB
- anaphylactic reaction after TCZ infusion is rare (0.6%).
- In case of TCZ hypersensitivity events, 50% are associated with AAB+
- Rituximab: 2.7 to 8.6% patients developed AAB
- AAB decreased levels of Ritux concentration but did not impact on clinical response.



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