Determining the Immunogenicity of Biologics: a Tricky Problem

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- **The theories expressed in this presentation are the views of the speaker and are not necessarily the views of UCB**

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Talk content

- **Background to immunogenicity**
- **Neutralising and non neutralising antibodies**
- **Immunogenicity assays**
- **Loading dose benefits**
- **Summary**

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The importance of understanding anti-drug antibodies

- In the past two decades, biological therapies, especially anti-tumour necrosis factor agents (anti-TNFs), have revolutionised the management of chronic inflammatory diseases, including rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), psoriasis and Crohn's disease (CD).
- Despite an acceptable responder rate of 60%–70% across these diseases, **there remains a substantial proportion of patients for whom treatment with anti-TNF agents leads to primary failure** (failure to demonstrate efficacy), **secondary failure** (loss of effectiveness over time despite an initial good response), or induces **significant side effects.**
- The **generation of anti-drug abs** is increasingly recognised as a **mechanism** explaining the failure of anti-TNF drugs in chronic inflammatory diseases

Vincent F et al. *Ann Rheum Dis*. 2013:72(2):165-78

Formation of anti-drug abs during Biologic Therapy

The term **'immunogenicity'** refers to the ability of a molecule to induce a specific cellular or humoral immune response, which is triggered by **differences between the structures** of foreign molecules and the body's natural proteins.[1]

Biological therapeutic proteins (such as monoclonal antibodies and receptor-linked antibodies) contain **unique sequences** that can elicit an immune response.[2] The antibodies formed during the immune response to therapeutic biologic proteins are known as **anti-drug antibodies** .[3]

Antibodies bind to epitopes displayed on the surface of antigens. Human antibodies contain a variable region which determines the antigen-binding specificity of the antibody. Antibodies are produced and secreted by activated cells of the immune system called B cells; the target of the antibodies produced is the specific antigen that activates a given B cell.[4]

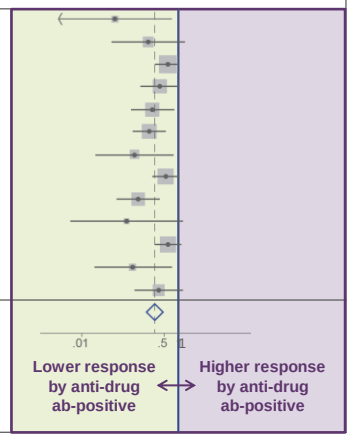
[1]Carrascosa J. *Actas Dermosifiliogr.* 2013;104(6):471-479
[2]Garcês S et al. *Ann Rheum Dis.* 2013;72(12):1947-1955
[3]van Schouwenburg P et al. *Nat Rev Rheumatol.* 2013;9(3):164-172
[4]Murphy K et al. *Janeway's Immunobiology.* 7th ed. 2008. pp. 15, 17, 111,120

Effects of Anti-Drug Antibodies on Clinical Efficacy

Development of anti-drug abs to IFX and ADA is Associated with Decreased Treatment Response

Effect of anti-drug ab-Positivity on Anti-TNF Treatment Response

Disease	Anti-TNF	Exposure Time (Months)	RR (95% CI)	% Weight
RA	ADA	6	0.05 (0.00, 0.70)	1.86
CD	ADA	12	0.23 (0.04, 1.32)	3.92
RA	ADA	6	0.56 (0.34, 0.94)	14.95
RA	ADA	3	0.39 (0.15, 0.96)	9.49
PSO	ADA	6	0.28 (0.10, 0.79)	8.41
RA	IFX	6	0.24 (0.11, 0.55)	10.69
AS	IFX	12	0.12 (0.02, 0.81)	3.51
RA	IFX	12	0.53 (0.29, 0.96)	13.49
CD	IFX		0.14 (0.05, 0.42)	8.05
UC	IFX		0.08 (0.01, 1.24)	1.87
RA	IFX	12	0.60 (0.31, 1.14)	12.87
SpA	IFX	12	0.11 (0.02, 0.71)	3.57
PSO	IFX	12	0.38 (0.12, 1.20)	7.32
Overall			**0.32 (0.22, 0.48)**	100.00

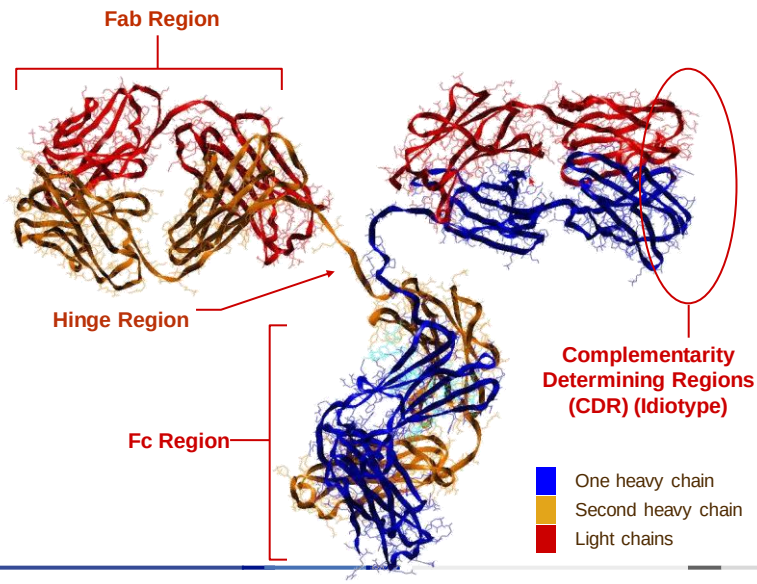


- A **meta-analysis** of 17 studies in RA, SpA, PSO and IBD
- Results show that, **overall, detectable anti-drug abs reduced the drug response rate by 68%** (RR=0.32, 95% CI=0.22–0.48)
- Significant between-study heterogeneity was observed (I^2=45.5%, p=0.037)

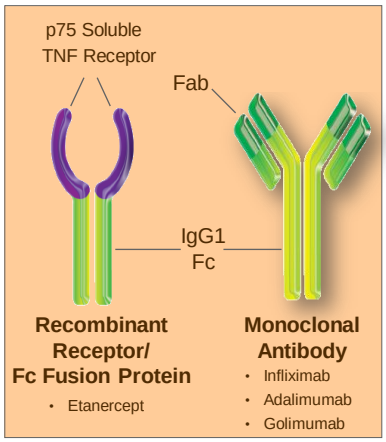
Weights are from random effects analysis
RR (risk ratio) and 95% CI (confidence interval) based on a random-effects model

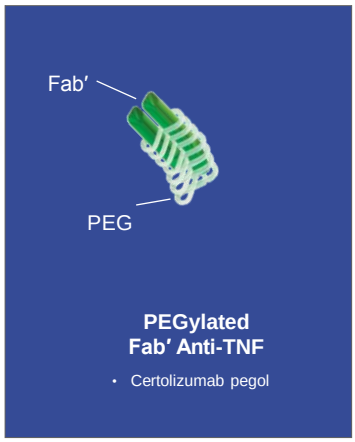
Adapted from: Garcês S et al. *Ann Rheum Dis.* 2013;72(12):1947-1955

The IgG Molecule: Key Features



Structure of the TNF-Blocking Agents





- All 4 reagents are bivalent, have an active isotype Fc
- Certolizumab pegol is structurally different: PEGylated, univalent, and does not have an Fc

Weir N, Athwal D, et al. *Therapy.* 2006;3:535-45

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Significance of CDRs

CDRs are made up of unique protein sequences in all antibodies
- Enables the antibody to bind to its specific antigen

The unique CDR protein sequence can provoke an immune response because it will be seen as 'foreign'
- This is called an anti-idiotype response

CDRs are therefore, the most immunogenic part of all antibodies

Immune responses to CDRs are likely to neutralise the activity of the antibody because they are seeing the part which binds to the antigen

Essential Immunology Eleventh edition P 38-40

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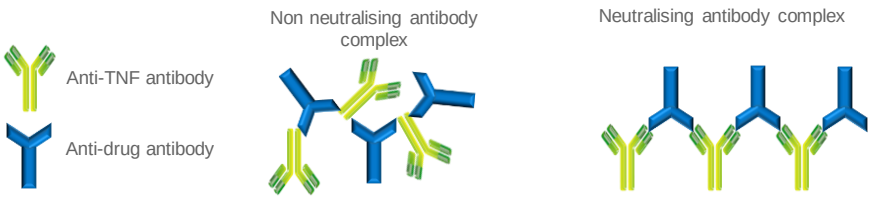
Neutralising and non neutralising antibodies will both lead to drug clearance

Neutralising antibodies will bind to the CDRs whereas non neutralising antibodies will bind to other parts of the molecule

Whenever neutralising or non neutralising antibodies bind to an antibody an immune complex will be formed which will lead to clearance of the antibody



Therefore, both type of antibodies will lead to clearance of the drug
- If the drug isn't present in the system it can't work!

. Matucci et al (2013) Clinical Dermatology 1: 77-80

Etanercept and immunogenicity

Etanercept is made up of human proteins
- Patients should be tolerant to these proteins

However, because it is a fusion protein the bit of sequence where the two proteins come together is novel[1]
- This would generate a non neutralising antibody but could lead to clearance of the drug

Etanercept
p75 TNF receptor/Fc
Fusion protein

Anti-drug antibody

Etanercept/anti-drug
Antibody complex

Any response to other parts of etanercept will be to a human protein
- Antibodies to the p75 TNF receptor could be dangerous

1. Matucci et al (2013) Clinical Dermatology 1: 77-80

Immunogenicity assays

Company assays all use a sandwich assay format but cannot be compared directly because they all have different internal standards[1]
- Conventional ELISA based assay

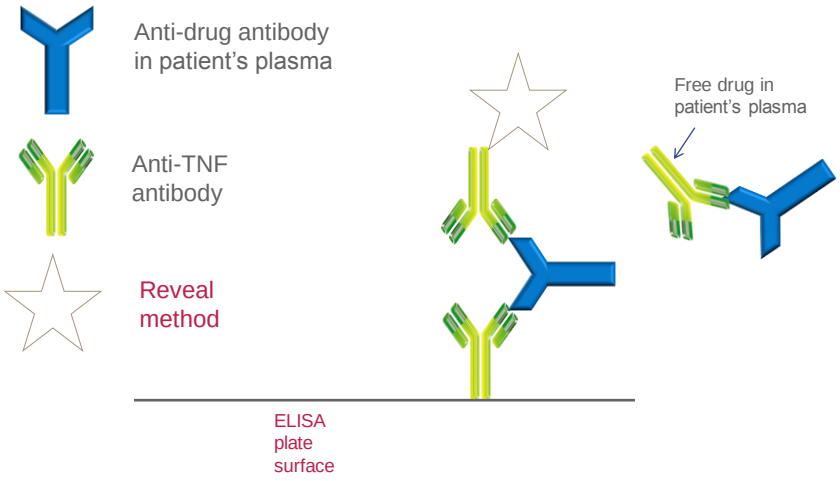
More sensitive assays have become available such as the antigen binding test [2]
- The anti-drug antibodies in the patient sera are bound to protein A beads

Bioassay based assays[3]
- Assay is based on TNF driven readout in a cell line

Other types of assays exist such as Prometheus' chromatography based assay[4]
- Rapidly evolving field with multiple companies providing assays with different formats

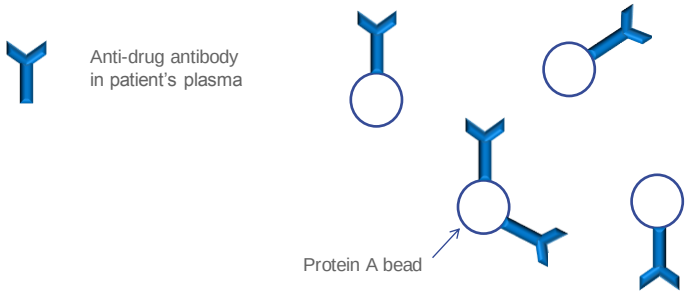
1. http://www.nature.com/jid/journal/v133/n9/pdf/jid2013287a.pdf
2. Hart et al 2011 J. Immunol. Methods 372:196-203L
3. Allemand et al (2011) J. Immunol. Methods 373: 229-239
4. Wang et al (2012) J. Immunol. Methods 382:177-188

Conventional immune response sandwich ELISA: Sensitive to the presence of free drug in the patient's plasma



Hart et al 2011 J. Immunol. Methods 372:196-203

Antigen Binding Test: less susceptible to the presence of free drug



Hart et al 2011 J. Immunol. Methods 372:196-203

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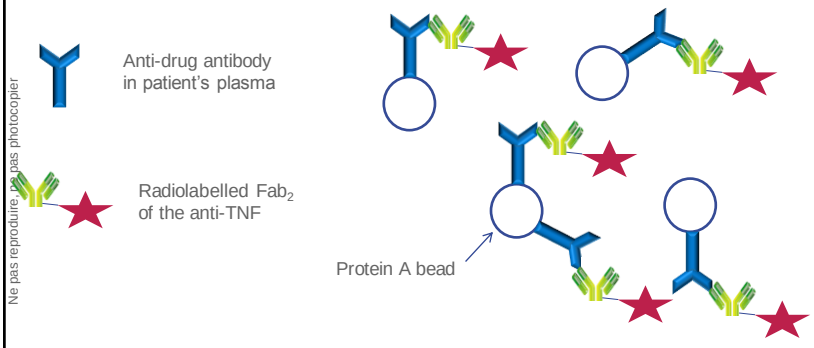
Antigen Binding Test: less susceptible to the presence of free drug



Hart et al 2011 J. Immunol. Methods 372:196-203

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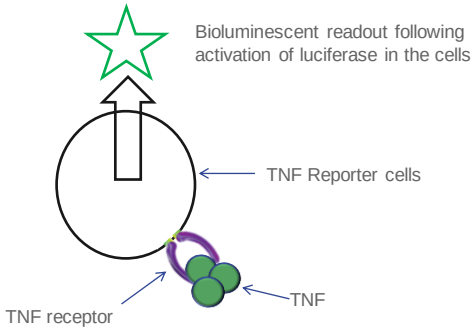
Bioassay based assays



Lallemand et al (2011) J. Immunol. Methods 373: 229-239

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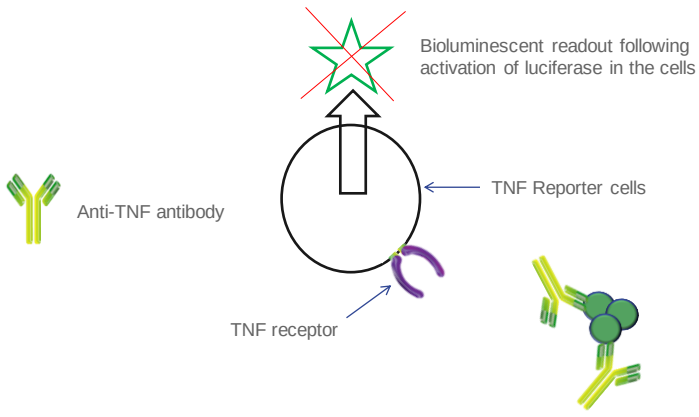
Bioassay based assays: Drug measurement assay



Lallemand et al (2011) J. Immunol. Methods 373: 229-239

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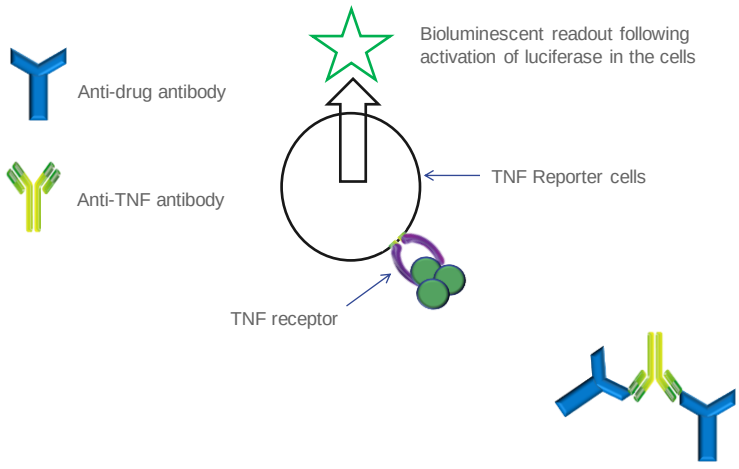
Bioassay based assays: Anti-drug ab measurement



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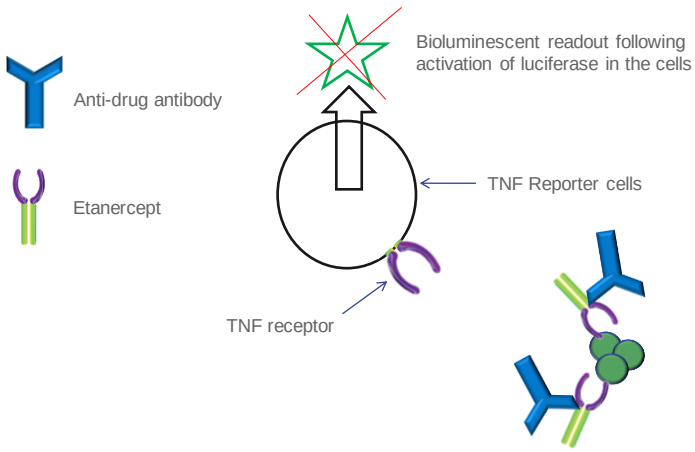
Bioassay based assays



This assay will only measure neutralising antibodies

Lallemand et al (2011) J. Immunol. Methods 373: 229-239

Loading Dose and Immunogenicity

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Loading Dose

- **Certolizumab pegol has a loading dose in both CD*, RA, axSpA and PsA**
  - 400mg dose at 0, 2 and 4 weeks
- **Loading dose is often not used by physicians for a number of reasons such as it increases the cost or the fact they are not aware of the label**
- **The potential advantage of the loading dose is that you reach the efficacious drug level more quickly which may lead to a rapid response[1]**
- **The rapid attainment of high drug levels may reduce immunogenicity due to a well described immunological phenomenon called high zone tolerance[2]**

CZP is not approved in Europe for CD

[1]Lacroix et al. *Clin. Pharm. Ther.* 2009;86:387-395
[2] Immunology Introductory Textbook, second edition 2005. P.145

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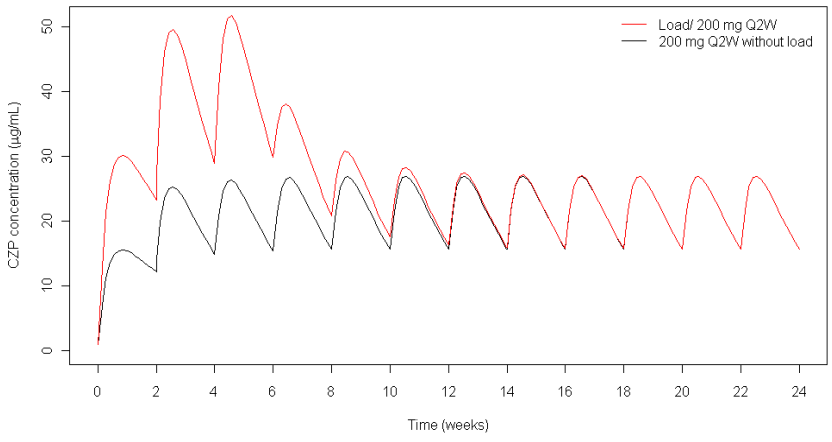
Effect of Loading Dose on CZP PK



Lacroix et al. *Clin. Pharm. Ther.* 2009;86:387-395

Effect of Loading Dose on Immunogenicity and Efficacy in J-RAPID and HIKARI

- J-RAPID and HIKARI assessed the safety and efficacy of CZP with and without MTX in Japanese patients
- Patients randomised to CZP in the double-blind phase received the loading dose of 400 mg at weeks 0, 2 and 4 and then maintenance therapy with 200 mg Q2W or 400mg Q4W
- Patients escaping from PBO to CZP at week 16 or completing the week 24 study on PBO received CZP 200 mg Q2W without loading dose in the OLE

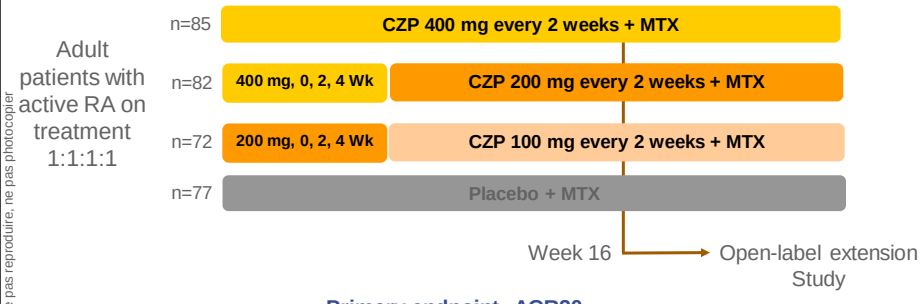
Takeuchi T, Yamamoto K et al ACR 2012; S563: Abstract No 1312
Takeuchi T, Yamamoto K et al ACR 2013; S989: Abstract No 2322

J-RAPID

J-RAPID Trial Design

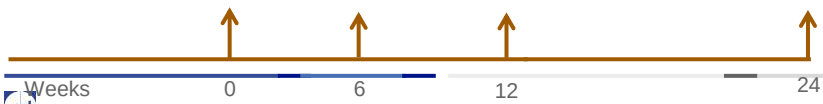
Objectives

A 24-week study to investigate the efficacy and safety of CZP + MTX in Japanese patients with active RA and an inadequate response to MTX



Primary endpoint: ACR20

Secondary endpoints: ACR 20/50/70 mTSS



UCB Data on File (Yamamoto et al. ACR 2011; Poster 1218)

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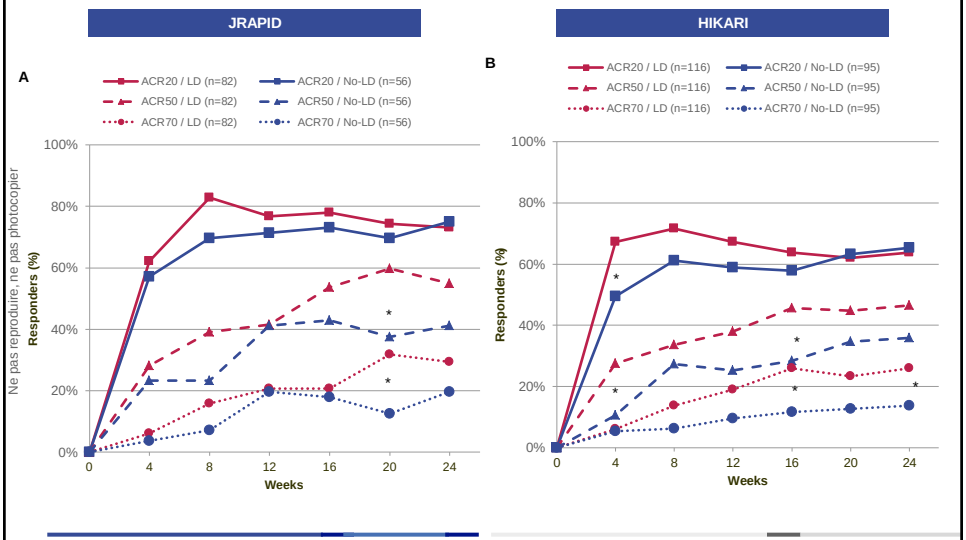
ACR Responses in the J-RAPID and HIKARI Trials



Takeuchi T, Yamamoto K et al ACR 2013; S989: Abstract No 2322

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Immunogenicity in the J-RAPID and HIKARI Trials

	J-RAPID			HIKARI		
	Total patients	Anti-CZP Ab positive patients		Total patients	Anti-CZP Ab positive patients	
	N	N	%	N	N	%
Loading Dose	82	1	**1.2**	116	18	**15.5**
No Loading Dose	61	3	**4.9**	99	27	**27.3**

LD: Loading dose

Takeuchi T, Yamamoto K et al ACR 2013; S989: Abstract No 2322

Summary

- All anti-TNFs can be immunogenic
- There are multiple assay types for immunogenicity which cannot be compared due to different formats and different positive controls
- It is more important to measure drug level than immunogenicity
- Loading dose can be an advantage for both increasing efficacy and reducing immunogenicity