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Clinical relevance of (unwanted drug-induced) immune responses

Presented at the EBF Focus Workshop by PD Dr. Arno Kromminga

20 September 2018

FDA Immunogenicity Guidance, 2016

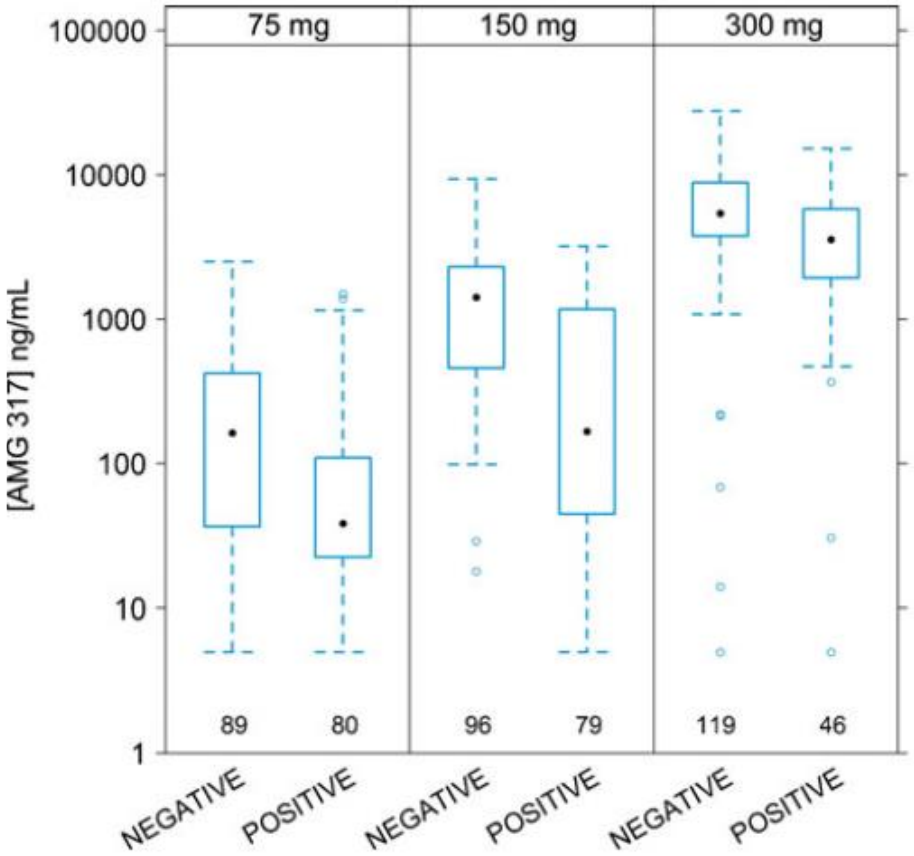
The sponsor should determine the sensitivity of the assay to have confidence when reporting immunogenicity rates. Assay sensitivity represents the lowest concentration at which the antibody preparation consistently produces either a positive result or readout equal to the cut point determined for that particular assay.

FDA recommends that screening and confirmatory ADA assays achieve a sensitivity of **at least 100 nanograms per milliliter (ng/mL).** Although traditionally FDA has recommended sensitivity of at least 250–500 ng/mL, recent data suggest that concentrations as low as **100 ng/mL may be associated with clinical events** (Plotkin 2010; Zhou, Hoofring, et al. 2013).

ADA characteristics and Characteristics

Concentration and characteristics of the ADA response observed following weekly administration of AMG 317

Higher ADA concentrations and later time points were associated with lower trough AMG 317 measurements.



Zhou L, Hoofring SA et al, AAPSJ, 2013

Determination of ADA Sensitivity

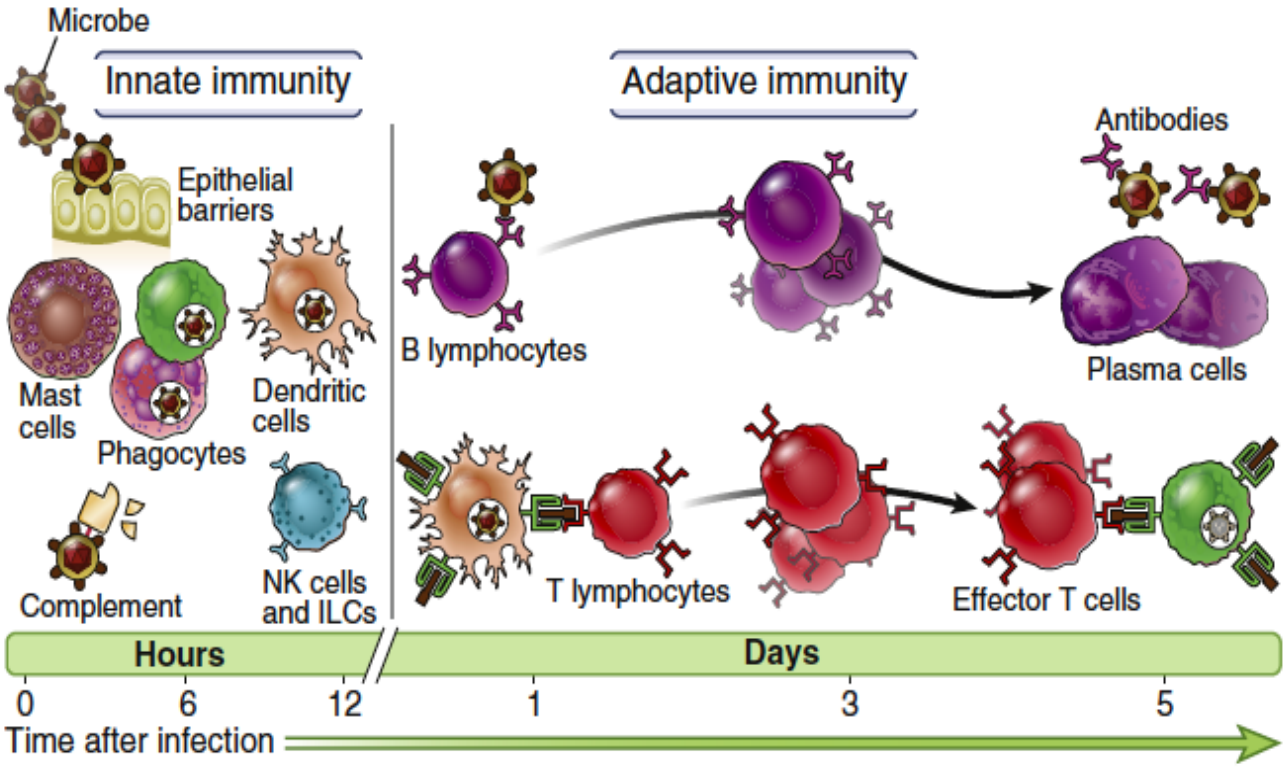
Assay Run	Linear Fit	Sigmoidal Fit	Asymmetric Sigmoidal Fit
Run1OP1	0,933	0,922	0,96
	0,761	0,615	0,615
Run2OP1	1,126	1,172	1,212
	1,048	0,980	0,998
Run1OP2	1,146	1,118	1,166
	0,942	0,756	0,759
Run2OP2	1,065	1,069	1,127
	0,997	0,891	0,938
Mean	1,002	0,940	0,972
SD	0,125	0,187	0,205
Sensitivity: mean + (t0.05df*SD) in ng/mL	1,3	1,4	1,6
LPC1: mean + (t0.01df*SD) in ng/mL	1,4	1,8	2,4

ADA sensitivity as low as low ng or even sub-ng range be achieved. The question needs to be discussed whether or not these high analytical sensitivities are needed or clinically relevant.

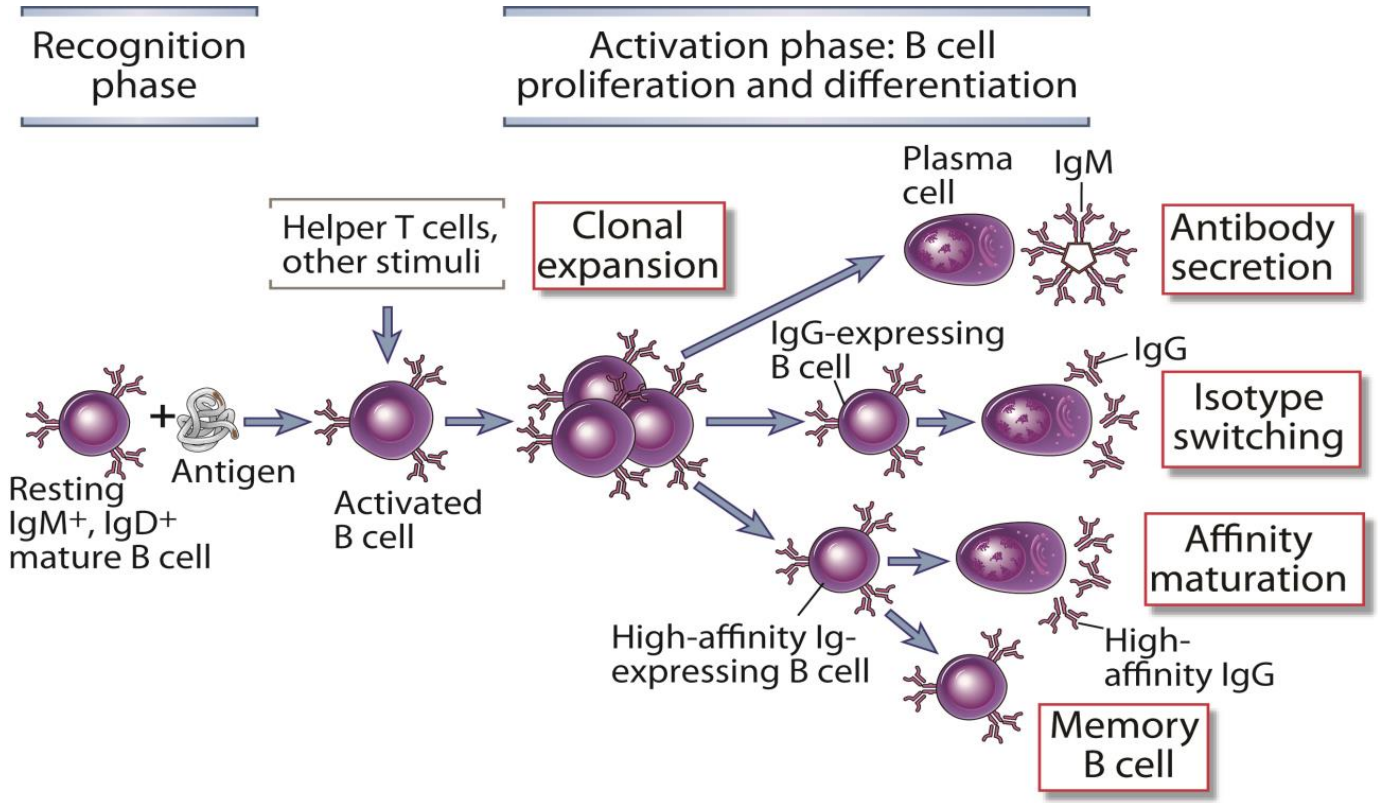
Induction of **Immune Responses**

The induction of immune response is **cascade of multiple steps and ultimately leads to highly specific antibodies and T cells.**

Abbas, Lichtman and Pillai, 2016



B Cell Activation and Antibody Production



The maturation of antibodies results in antibodies with different binding affinities and functionalities.

Abbas, Lichtman and Pillai, 2016

Natural **Antibodies**

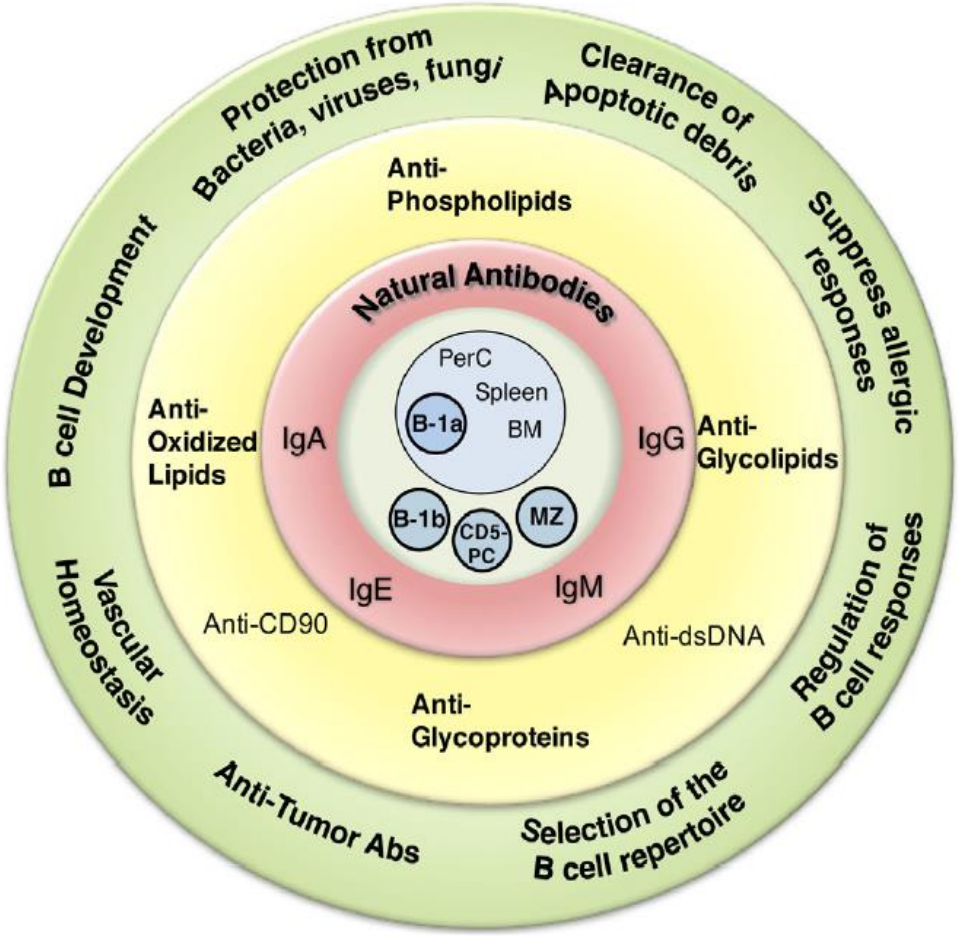
Natural antibodies are pre-immune antibodies generated in the absence of exogenous antigenic stimulation.

Natural antibodies

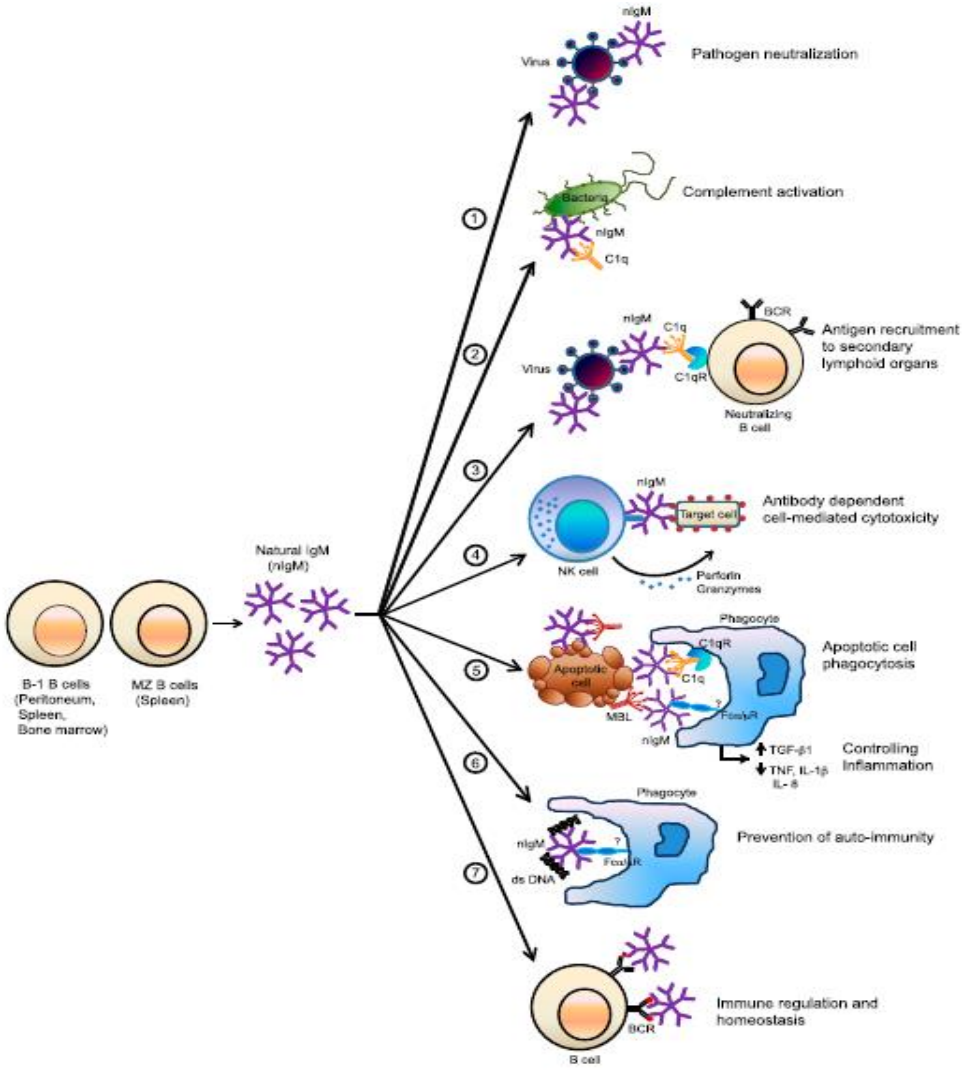
- ✓ have the ability to exert a protective or regulatory function
- ✓ show a pre-existing/immediately immune responsive.

Green: various functions	Red: isotype
Yellow: epitope recognition	Blue: cells

Holodick NE et al, Front Immunol, 2017



Diverse Roles of Natural IgM Antibodies

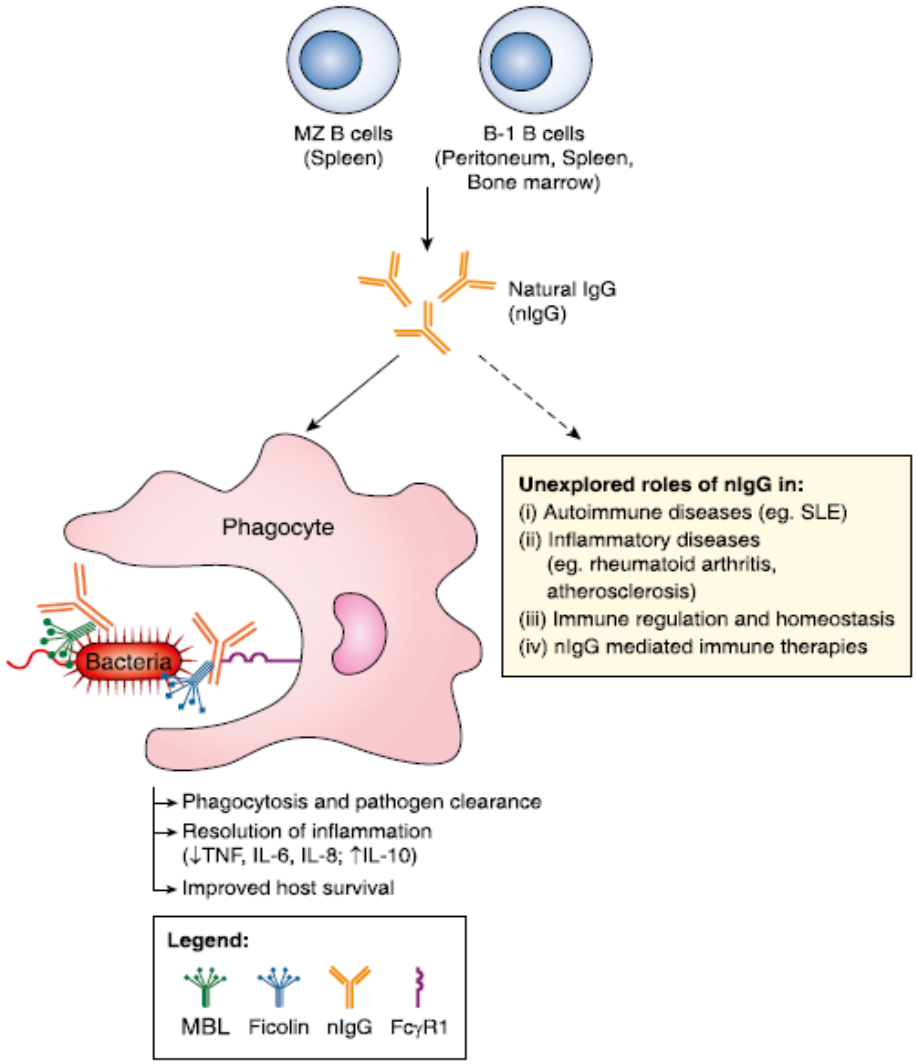


Natural IgM plays a role in:

- ✓ Direct pathogen neutralization
- ✓ Classical complement activation
- ✓ Ag recruitment and priming of subsequent TI adaptive immunity
- ✓ Ab-dependent cell-mediated cytotoxicity
- ✓ Apoptotic cell phagocytosis
- ✓ Clearance of DAMPs
- ✓ B cell homeostasis

Panda S & Ding JL, J Immunol, 2015

(Possible) Roles of Natural IgG & Natural IgG Antibodies

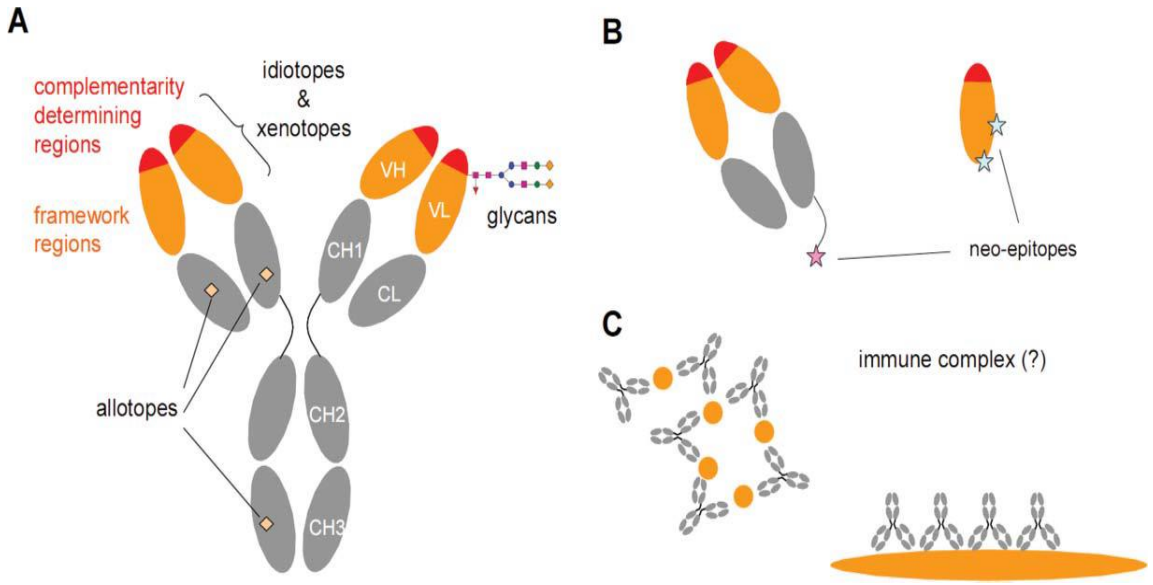


a. **Pathogen recognition and clearance,** thus controlling inflammation by regulating the production of cytokines

b. **Role in Health and Disease:**
   - ✓ Controlling or exacerbating autoimmune diseases,
   - ✓ Ameliorating inflammation,
   - ✓ Immune regulation and homeostasis,
   - ✓ Development of safer and more effective immunomodulators.

Panda S & Ding JL, J Immunol, 2015

Pre-existing Antibodies



Antibodies Directed Towards:

- ✓ Idiotype (CDR, FR)
- ✓ Isotype
- ✓ Allotype
- ✓ Heterophilic antibodies
- ✓ Hinge region
- ✓ Carbohydrates

van Schie, Wolbink, Rispens,mabs, 2015

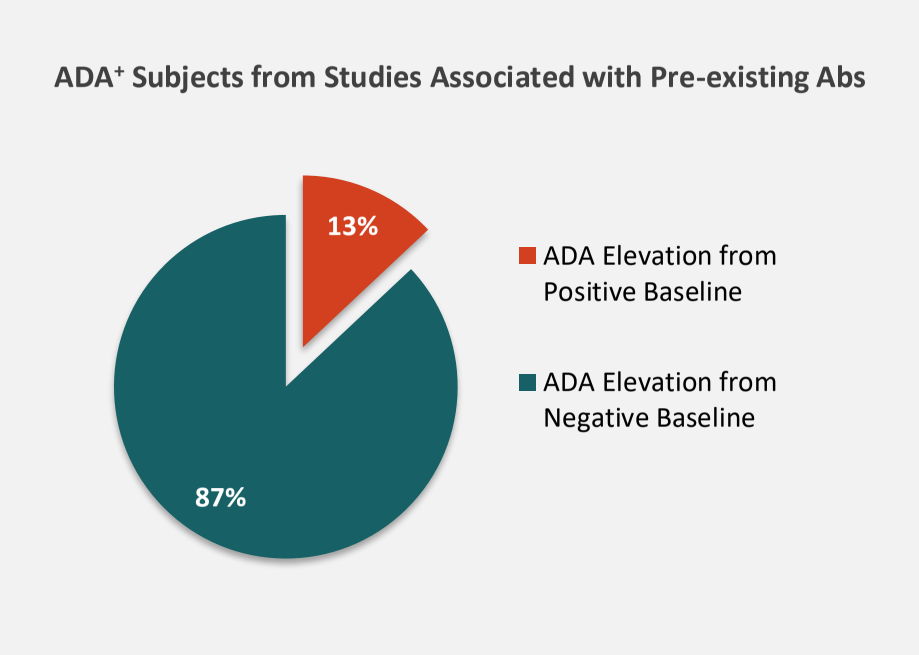
Clinical Relevance of **anti-PEG Antibodies**

Product	PEG conjugation	Study population	Detection of pre-existing anti-PEG	Detection of treatment induced anti-PEG	Clinical impact of pre-existing anti-PEG	Clinical impact of treatment induced anti-PEG
Pegloticase™ (PEG-porcine uricase)	10-KDa PEG X9 per each of 4 protein subunits. Total of 360 methoxy PEG (mPEG)	Patients with refractory gout	Yes	Yes	Rapid clearance, loss of efficacy, increased risk of infusion reactions	Rapid clearance, loss of efficacy, increased risk of infusion reactions
PEG-asparaginase	5-KDa mPEG	Acute lymphoblastic leukemia patients	Yes	Yes	Inconclusive	Rapid clearance
PEGASYS™ (PEG-IFN-α2a)	40-KDa single-branched bis-mPEG	HCV-infected patients	Yes	Yes	No	No
PEG-IFN-β1a	20-KDa mPEG	Multiple sclerosis	Yes	Yes	Unknown	Unknown
Peg-IFN-γ	20-KDa linear mPEG	HCV-infected subjects	Yes	Yes	No	No
PEG-intron (PEG-IFN-α2b)	12 KDa, mPEG	HCV-infected patients	Yes	Yes	No	No

Gorovits B et al. , AAPSJ, 2016

Prevalence and Consequence of Pre-existing AB

	Percentage	Number of Subjects
In all study subjects	10.8%	(103/950)
In healthy volunteers	3.6%	(3/84)
In all disease populations	11.5%	(100/866)
In disease populations excluding RA	8.5%	(38/446)
In RA patients	14.8%	(62/420)

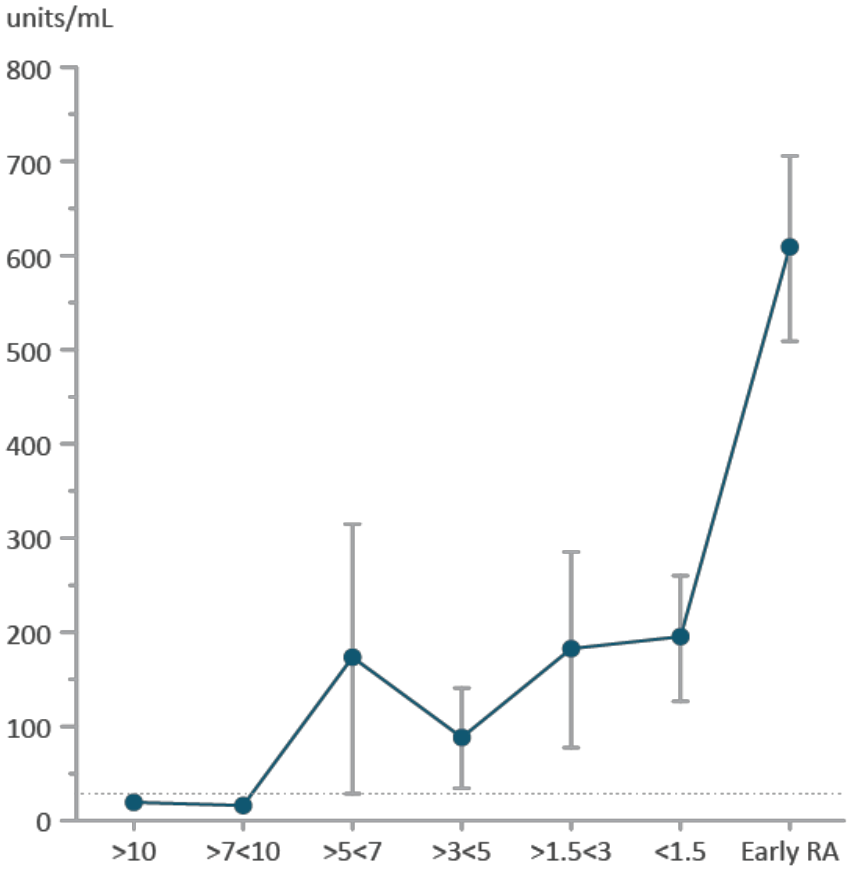


a. 10.8% of all study subjects had detectable pre-existing Abs across studies.

b. 13% of subjects with post-treatment ADA were positive for pre-existing antibodies.

Xue L & Rup B, AAPSJ, 2013

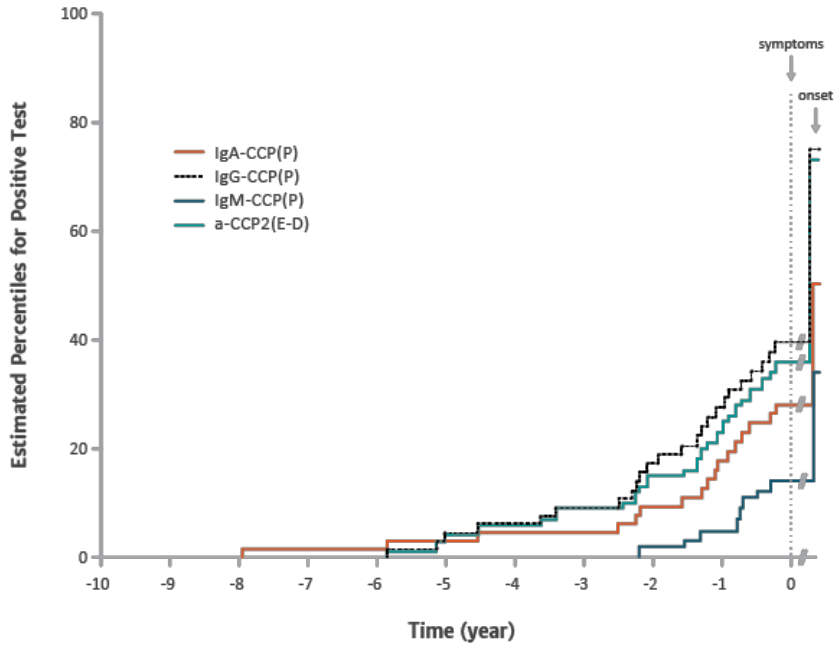
Anti-CCP AB Detection Prior to the Disease Onset



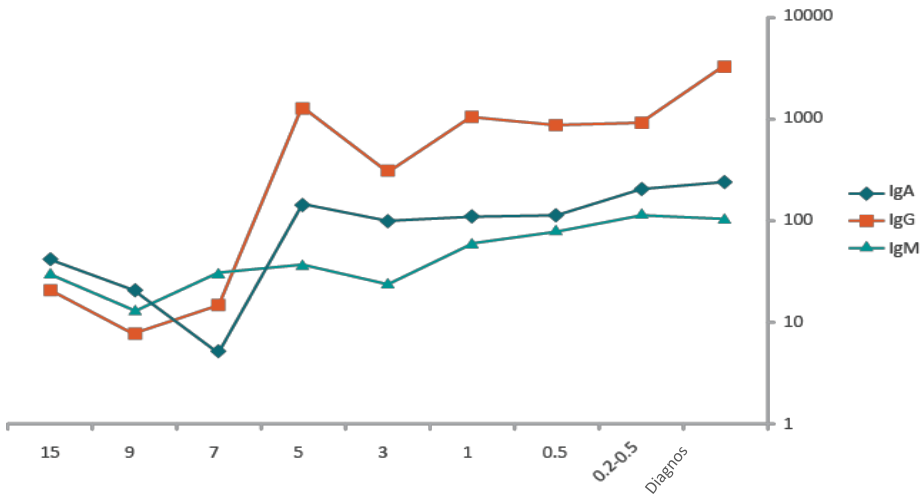
	Sens (%)	Spec (%)	PPV (%)	NPV (%)
RA Patients	34	98	82	86
>1.5 years before symptoms	25	98	80	84
<1.5 years before symptoms	52	98	85	89
Early RA	70	98	91	93

Rantapää-Dahlqvist S et al. , 2003

Predictive Antibodies Against CCP (in RA)



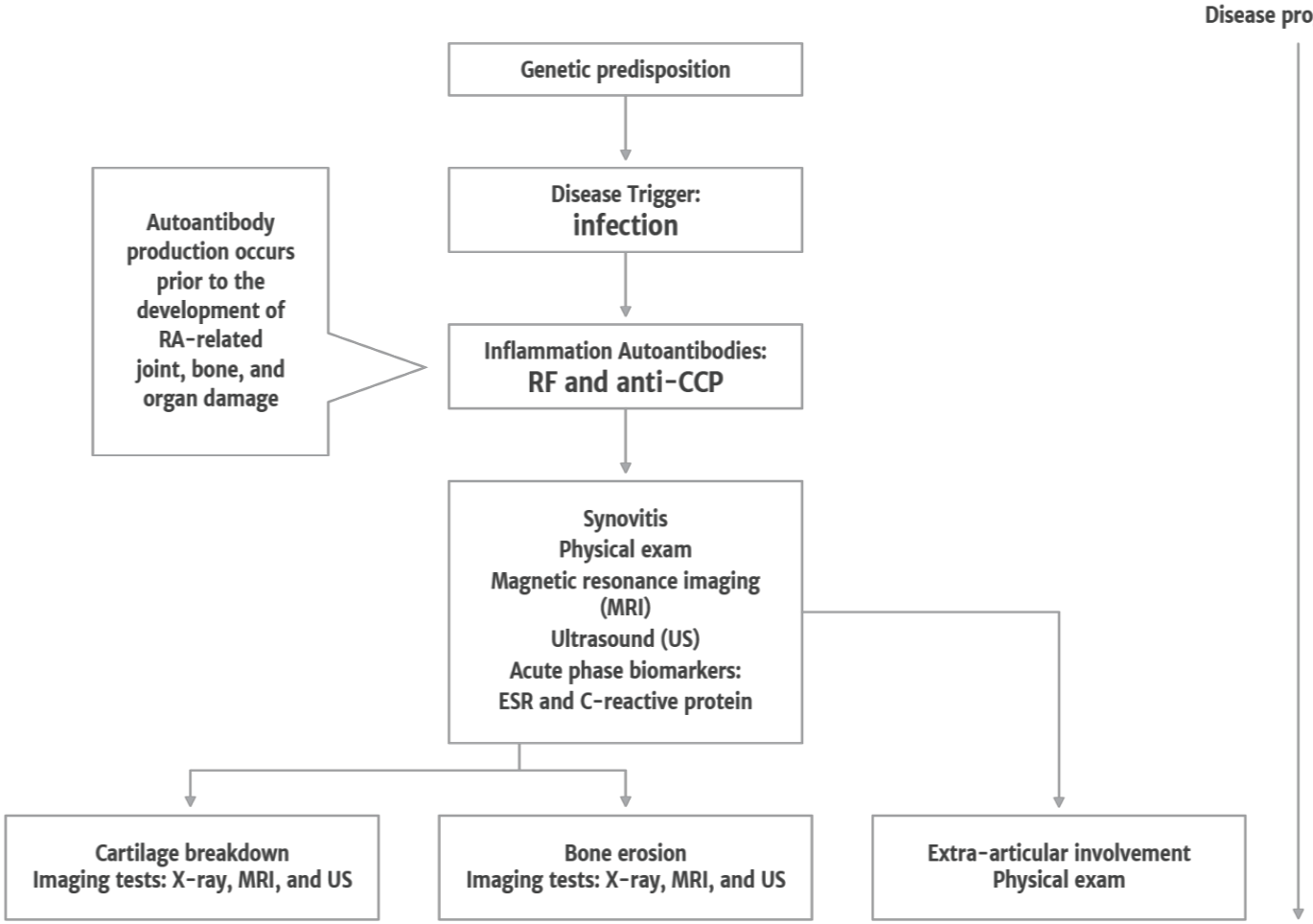
Accumulated **percentage positive samples** analyzed before onset of symptoms and at diagnosis.



Antibody levels, as **percentage of cut-off values** before and at disease onset

Kokkonen et al. Arthritis Research & Therapy 2011

Time Course of Clinical RA Onset



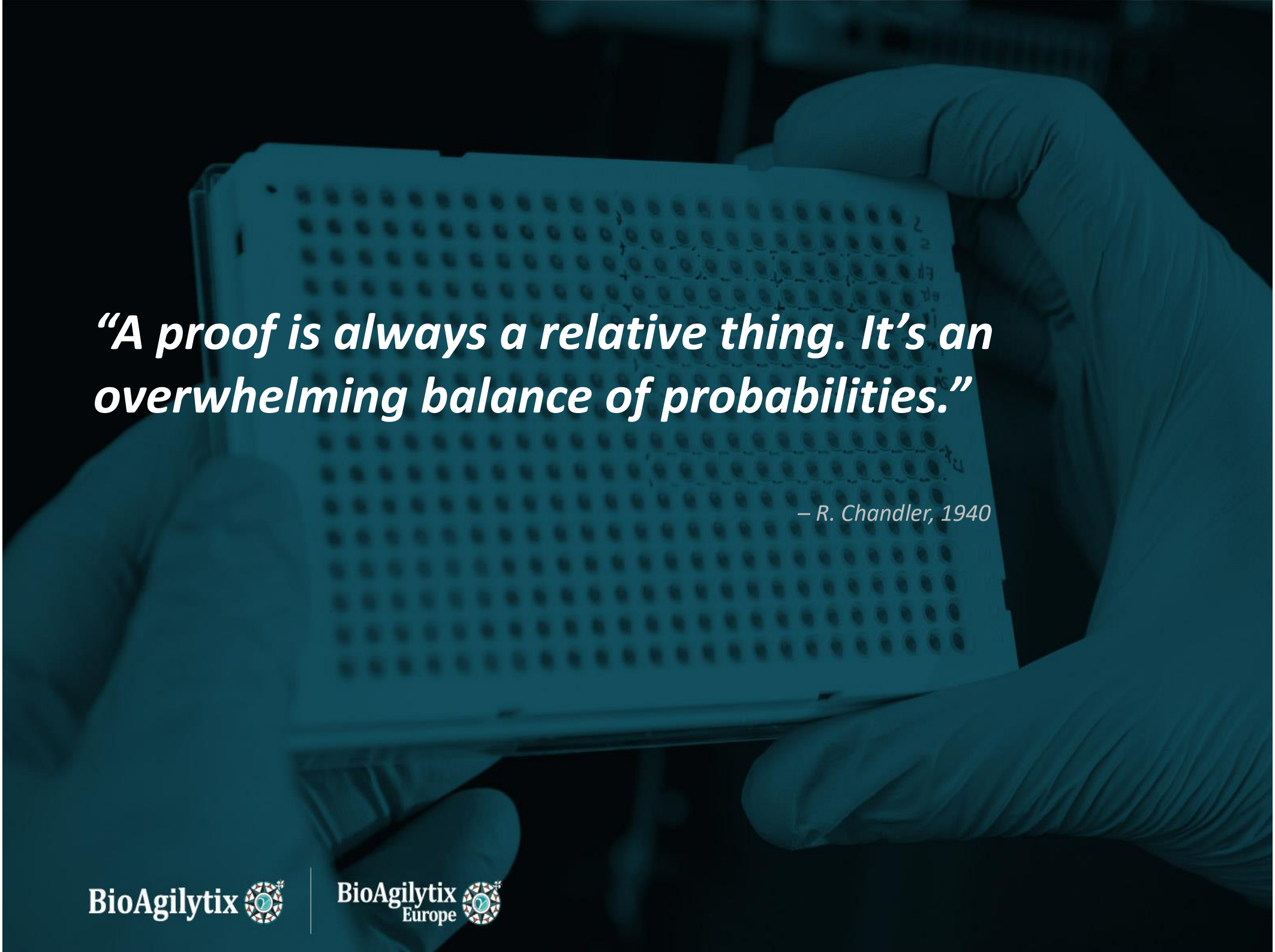
Anti-CCP antibodies in the serum of patients are present as many **as 12 to 14 years** prior to the development of RA. In these studies, **34%–40%** of the RA patients had anti-CCP+ results prior to disease onset

Taylor P et al. Autoimmune Dis, 2011

Conclusion

- ✓ Immune responses against self or foreign **may lead to the formation of detectable antibodies.**
- ✓ It is unclear whether **pre-existing Abs** may increase the risk for drug-induced ADA.
- ✓ Antibody formation **often precedes the clinical onset** of immune-mediated diseases.
- ✓ Antibody assays **cannot be too sensitive.**
- ✓ A **careful and thorough data interpretation is needed** which takes into account the clinical manifestation and clinical relevant biomarkers (including PK).
- ✓ The kinetics and type of antibody responses should be monitored to **assess the risk of developing a treatment-emergent immune responses.**
- ✓ Post-approval ADA and drug patient monitoring **should be mandatory.**

Outlook



"A proof is always a relative thing. It's an overwhelming balance of probabilities."

– R. Chandler, 1940

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