

Strategies to Assess the Neutralizing Capacity of ADAs Against Biopharmaceuticals

EBF - Focus Workshop, September 2016

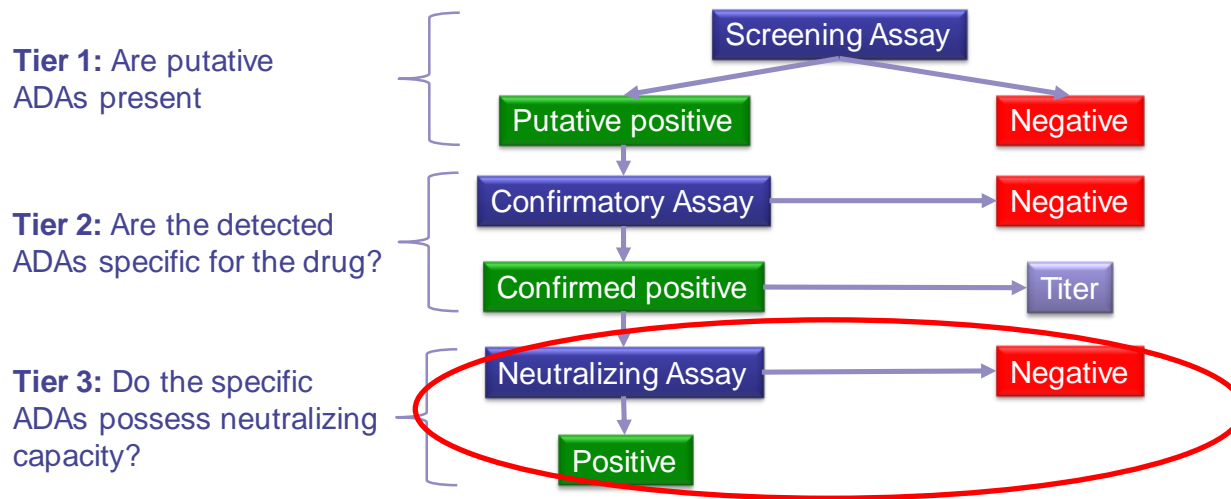
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Assessment of NABs

Current Situation

- There is a strong tendency within biopharmaceutical industry to replace dedicated neutralizing (NAb) assays by an integrated assessment of ADAs and PK/PD
- However, authorities are rather hesitant and still requesting to stick to the standard 3-tiered approach

EMA: "This includes a screening assay..., a procedure for confirming the presence of antibodies...followed by *functional assays for the assessment of the neutralizing capacity of antibodies...Specific and sensitive in vitro methods are needed for detection (of NABs)*" (EMEA/CHMP/BMWP/14327/2006 Rev. 1)



Under which circumstances can an integrated ADA and PK/PD assessment take the place of *in vitro* NAB assays???

Assessment of NABs

Why.....?



- In general ADAs can lead to clinical consequences
 - Impact on efficacy
 - Impact on safety
- NABs are thought to be primarily responsible for triggering clinical effects
- However, only few of these clinical consequences are mediated by neutralizing antibodies

Clinical Impact of ADAs	Root Cause
Reduced efficacy	“Clearing“ antibodies / NABs
Exaggerated pharmacology	“Sustaining“ antibodies
Infusion reactions	Complement or immune cell activation; not NAb mediated
Type I hypersensitivity	Drug specific IgE (non neutralizing)
Type III hypersensitivity	Drug specific IgG (non neutralizing)
Immune deficiency syndrome	NABs (cross neutralization of non-redundant endogenous counterpart)



Characterization of the ADA Response (I)

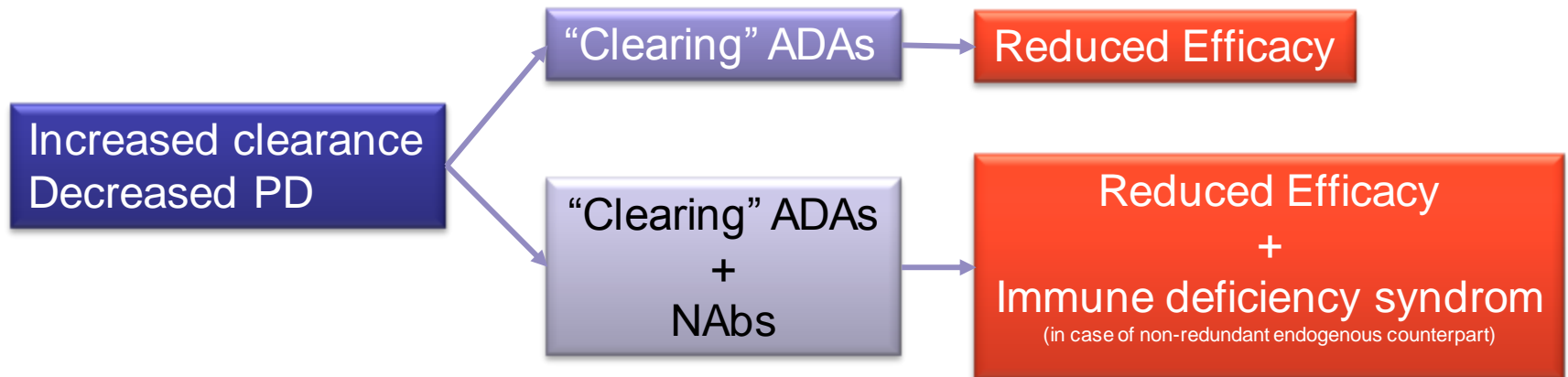
- Is a combination of PK/PD and ADA status sufficient to “predict” the NAb status and to fully characterize the ADA response?

ADA Status	NAb status	Clearance	PD	ADA Category
positive	negative	normal	normal	“Binding“ ADAs
positive	negative	increased	decreased	“Clearing“ ADAs
positive	negative	decreased	increased	“Sustaining“ ADAs
positive	positive	normal	decreased	NAbs
positive	positive	increased	decreased	“Clearing ADAs / NAbs
positive	positive	decreased	decreased	“Sustaining“ ADAs /NAbs

- Overall an integrated assessment of PK/PD and ADA is able to “predict” the NAb status
- It cannot discriminate if an observed increased clearance/decreased PD is due to “clearing” antibodies only or the combination of “clearing” and neutralizing antibodies

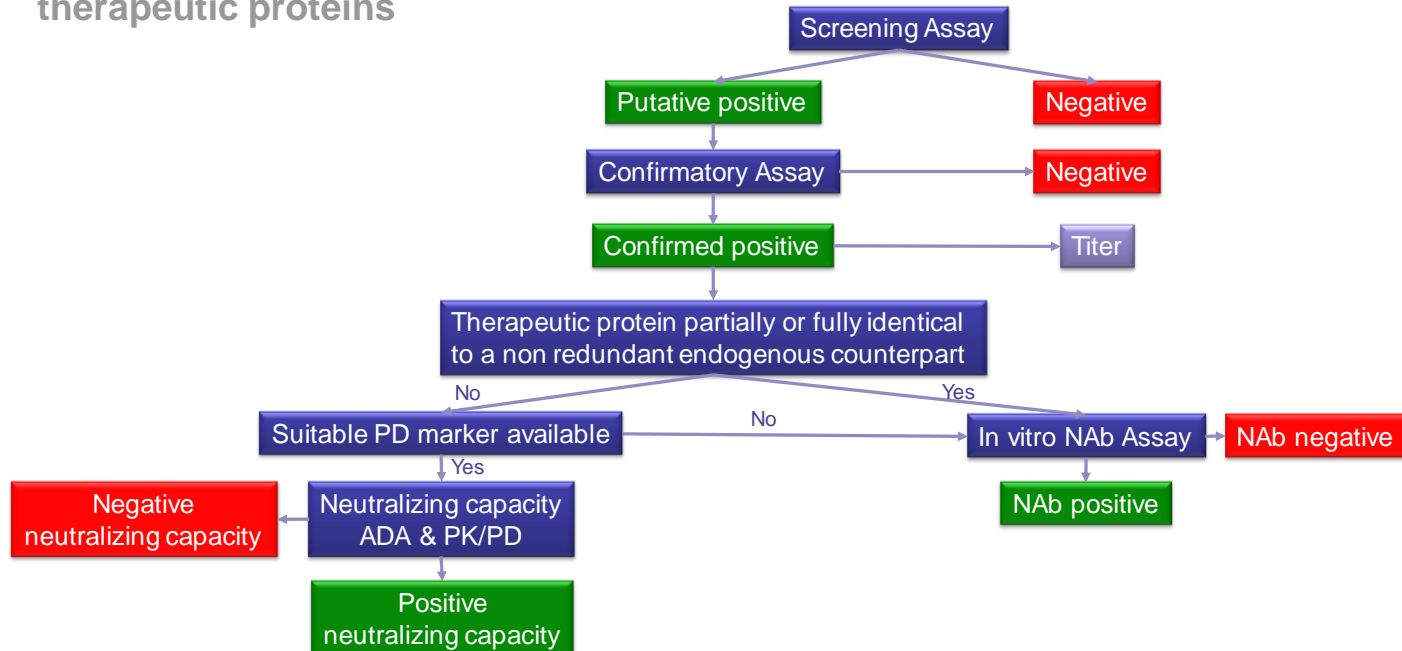
Characterization of the ADA Response (II)

- Increased clearance and/or decreased PD is expected to impair the efficacy of a therapeutic protein (irrespective of the presence of NABs)
- In presence of NABs an immune deficiency syndrome might occur (in addition to impaired efficacy) if the therapeutic protein is partially or fully identical to a non redundant endogenous counterpart
 - For these therapeutic proteins dedicated in-vitro NAb assays are warranted (see next slide)



Revised 3-Tiered Approach

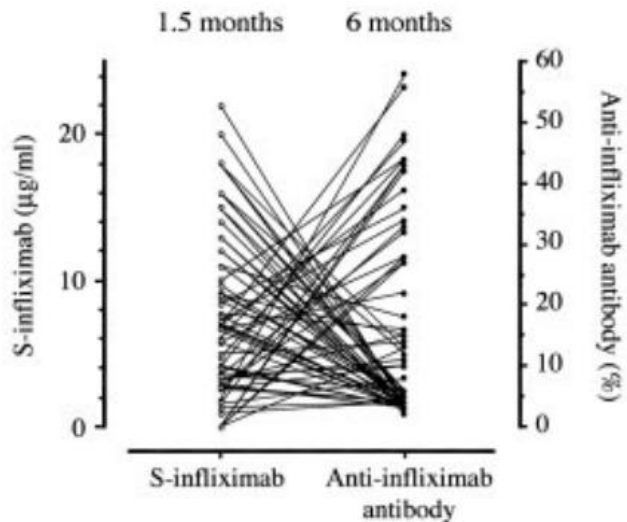
- For therapeutic proteins which are neither partially nor fully identical to non-redundant endogenous counterparts it is not important, if an observed decreased efficacy is due to clearing and/or neutralizing antibodies
 - For these therapeutic proteins it is deemed sufficient to use an integrated assessment of ADA + PK/PD to assess the neutralizing capacity of ADAs
- For therapeutic proteins which do possess unique endogenous counterparts, neutralizing antibodies represent a potential safety issue (cross-neutralization)
 - It is important to confirm the presence/absence of neutralizing antibodies for these therapeutic proteins



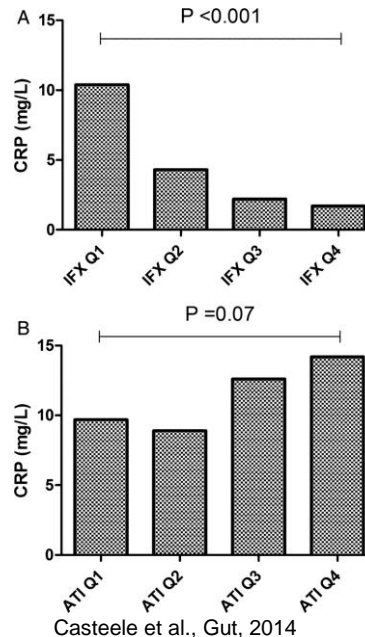
Example: Enhanced Clearance / Decreased PD

Anti-TNF Monoclonals

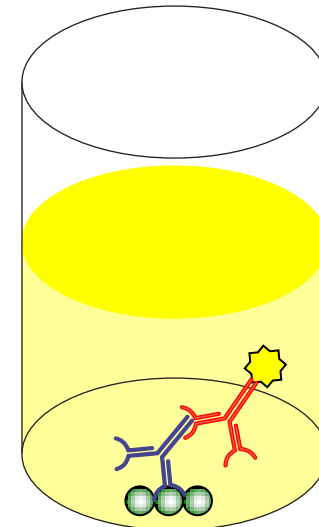
- A major contributor to secondary response failure of anti-TNF monoclonals is immunogenicity
 - Trough serum levels of anti-TNF monoclonals decline as soon as ADAs appear (due to neutralizing and/or “clearing” ADAs)
 - Reduction of C-reactive protein (CRP) concentration is decreased in ADA positive subjects
- An “active” PK assay format is applied to measure concentrations of anti-TNF monoclonals
 - PK Assay is sensitive to clearing and neutralizing antibodies



Bendtzen et al., Arthritis & Rheumatism, 2006



Castele et al., Gut, 2014



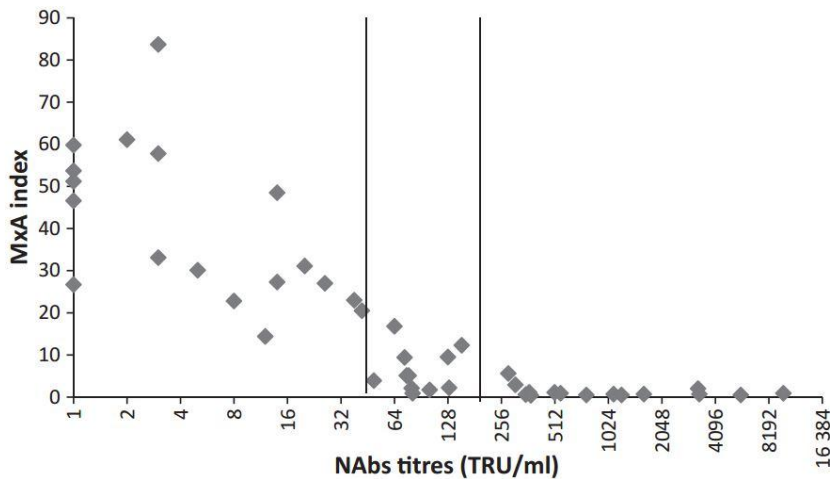
Labeled anti-human Fc
 Infliximab
 Immobilized TNF-alpha

➡ No in-vitro NAb assay required to assess/characterize the immunogenicity of anti-TNF monoclonals

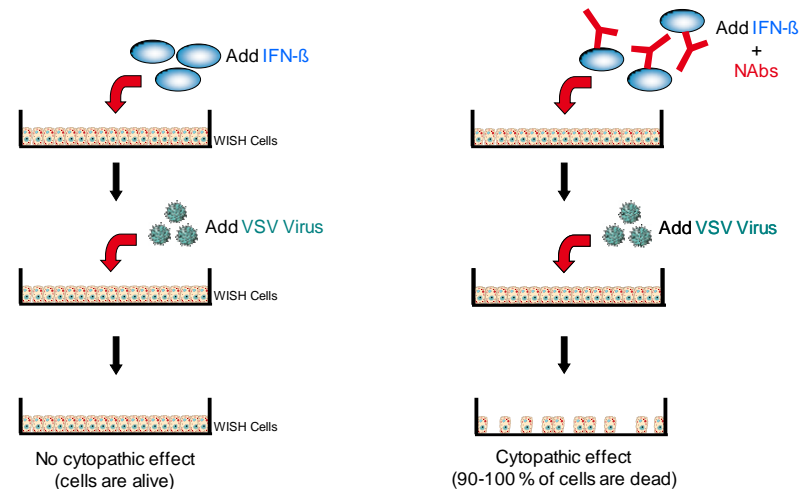
Example: Normal Clearance / Decreased PD

Interferon-beta (IFN beta)

- Neutralizing antibodies during interferon-beta treatment of multiple sclerosis are associated with reduced clinical efficacy
 - NAb are generally determined using *in vitro* assays detecting neutralization of virus growth inhibition by IFN beta (Cytopathic Effect (CPE) Assay)
- Data indicate that analyzing Myxovirus resistance protein A (MxA) expression is a sensitive indicator of IFN beta neutralization and correlates well with *in-vitro* NAb results
 - The CPE assay does not necessarily measure the loss of biologic activity
 - A decrease in MxA protein expression level usually precedes the detection of NABs



Jensen et al., European Journal of Neurology, 2012



➔ MxA expression seems to better reflect the neutralizing capacity of ADAs than the CPE assay

Summary & Conclusion

- There are instances in which NAb results do provide data that, with ADA & PK/PD alone, are not sufficient for risk management of patients
 - No suitable PD marker or clear-cut clinical endpoints available
 - The presence of NAb is associated with a high safety risk for patients (therapeutic proteins partially or fully identical to a non-redundant endogenous counterparts)
 - However, in other cases, dedicated in-vitro NAb assays are not needed to interpret immunogenicity data adequately
 - For anti-TNF monoclonals the combination of ADA titers, PK and clinical endpoints are used successfully
 - For IFN beta, NAb detected in the CPE assay do not always correlate with decreased clinical efficacy. Although in-vitro NAb assessment is routinely performed, it does not seem to be essential. It might therefore be replaced by MxA protein expression being a sensitive indicator of IFN beta neutralization
 - Further discussion with authorities are needed in order to gain a common understanding on this topic
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THANKS!!!!!!

