Medicines & Healthcare products Regulatory Agency

NIBSC
Confidence in Biological Medicines

Harmonisation of Immunogenicity Testing: The EU Perspective

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European Bioanalysis Forum, Sep 2018

Disclaimer

The views and opinions expressed in this presentation are entirely my own and should not be misconstrued as those representing any regulatory authority

FDA guidance on immunogenicity of therapeutic proteins

2014 – Immunogenicity assessment for therapeutic protein products

2016 – Assay Development and Validation for Immunogenicity testing of therapeutic protein products (Draft)

Final version (expected 2018)

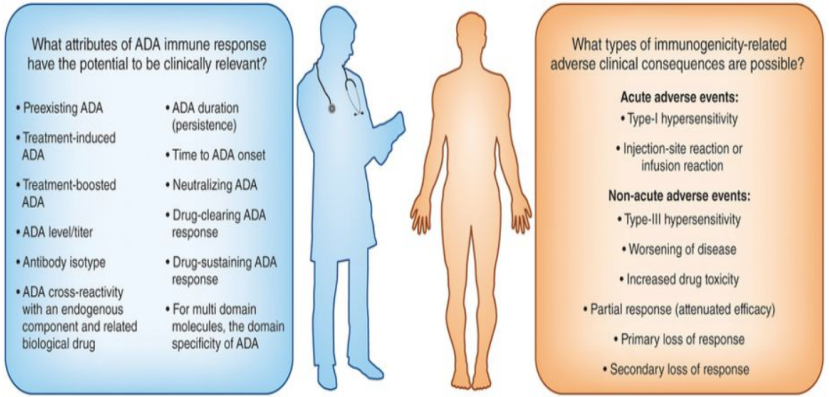
EMA guidance for immunogenicity of therapeutic proteins

- **2007** - Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006) → revision
- **2017** – Guideline on Immunogenicity assessment of ~~biotechnology-derived~~ therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1) → **1st Dec 2017**
  - risk-based approach; assays – specific information e.g., complex therapeutics
  - Comparative immunogenicity – manufacturing changes, biosimilars
  - Integrated summary of immunogenicity
- **2012** - Immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use (EMA/CHMP/BMWP/86289/2010)
- Biosimilars guidelines http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000043.jsp&mid=WC0b01ac05800240cb

Harmonised Approach to Immunogenicity Testing

- EMA – general and pragmatic, adopting ‘industry practice’ where possible and harmonizing with FDA
- EMA – no specific guidance but ‘Guideline on bioanalytical method validation’EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**
- FDA – prescriptive but useful, aligned with industry, adopting Integrated Summary and Life-cycle approach
- FDA - specific guidance on ‘Assay development and validation’

Concepts and principles are generally well-aligned
Deliver meaningful and clinically relevant immunogenicity results for patient safety and informed prescribing



Nat Biotechnol. 2015 Apr;33(4):334-6. doi: 10.1038/nbt.3181.
The quintessence of immunogenicity reporting for biotherapeutics.
Shankar G[1], Arkin S[2], Devanarayan V[3], Kromminga A[4], Quarmby V[2], Richards S[5], Subramanyam M[1], Swanson S[5]

EMA Immunogenicity Guideline (2017)

To detect clinically significant immunogenicity, if any

Harmonise immunogenicity evaluation and reporting

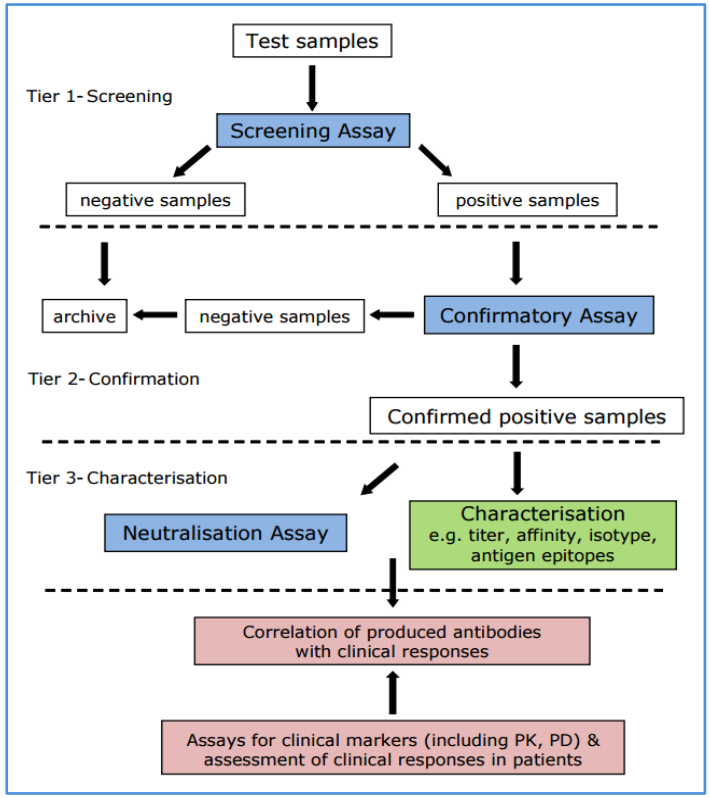
‘Developing an integrated analysis strategy relevant for the intended treatment plan is critical for elucidating the clinical relevance of immunogenicity data’

EMA Immunogenicity Guideline (2017)

Integrated planning, analysis and assessment

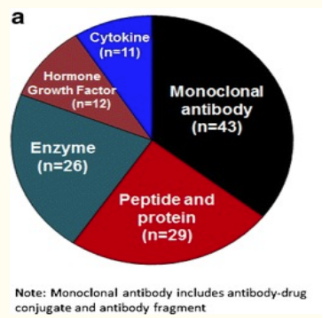
- Analysis of risk factors
- Risk-based immunogenicity testing
  - Well-designed studies
  - Sampling strategy (ADA, therapeutic)
  - Multi-tiered approach
- Data on immunogenicity
- Integrated analysis of clinical impact
- Conclusion on the risk of immunogenicity

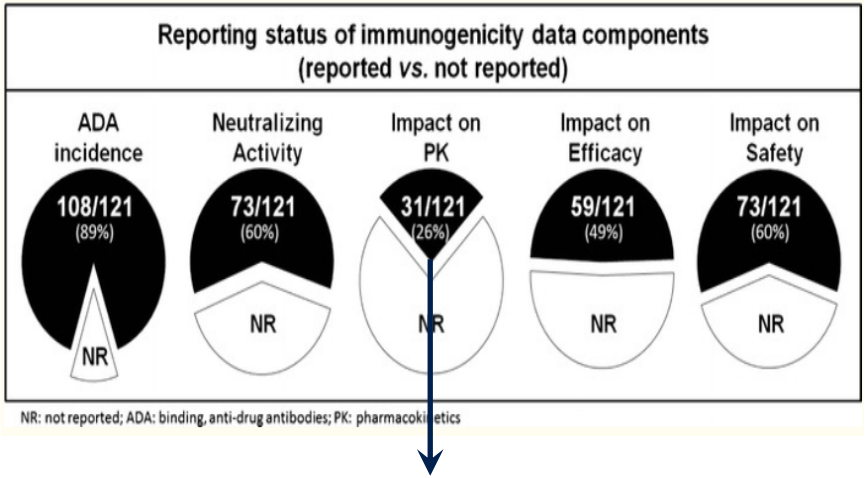
Integrated Summary of immunogenicity



Immunogenicity Testing

Review by FDA of prescribing data





ADA impact on pharmacokinetics using model-based methods. Our findings support that pharmacokinetic exposure is more sensitive than efficacy endpoints for evaluating ADA effects. A decrease in drug concentration due to formation of ADA during treatment can serve as an early indicator for potential reduced efficacy occurring at a later time.

AAPS J. 2016 Mar; 18(2): 395–403.
Published online 2015 Dec 31. doi: 10.1208/s12248-015-9857-y
PMCID: PMC4779104
PMID: 26721560

Evaluating and Reporting the Immunogenicity Impacts for Biological Products—a Clinical Pharmacology Perspective

Yow-Ming C. Wang,[a] Jie Wang, Yuen Yi Hon, Lin Zhou, Lanyan Fang, and Hae Young Ahn

29/31– effect on PK was stated; 2- inconclusive; 15/31 – impact on efficacy not reported. Overall, 16 products with ADA impact on PK & efficacy data

8/16 – drug clearance ↑ & efficacy ↓

6/16 – no change in clearance or efficacy

2 – drug sustaining ADA with high exposure but not ↑ efficacy

Example: Benralizumab (Fasenra)

- Humanised, afucosylated mAb - IL-5Rα subunit on basophils, eosinophils and induces their apoptosis in the presence of NK cells via enhanced ADCC
- Indication - add-on maintenance therapy for severe asthmatic adults (eosinophilic phenotype)
- Phase III – 2 dosing frequencies; 30 mg sc every 4 weeks vs every 4 weeks for the 1st three doses, then every 8 weeks thereafter
  - 3-tiered testing – screening, confirmatory and titre, NAb assay
  - ADA +ve - Baseline 2%, post-treatment 7-14% study based (boost & new btw 8-16 wks); median titres peaked ~400; very high titres >25,600 in 0.5% patients
  - 68-80% were NAbs and persistent; high median titres (ADA and nAb titres)
  - ADA incidence slightly higher and increased NAbs with low freq vs 4-week regimen
  - ADAs impacted trough levels ↓ and eosinophils ↑ to pre-treatment levels (rare)
  - No clear effect of ADAs on efficacy/safety incl hypersensitivity reactions.

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Public_assessment_report/human/004433/WC500245333.pdf

Example: Benralizumab (Fasenra)

- Further data on the long-term impact of persistent neutralising ADAs will be provided from the extension trials (2 studies) as part of phamacovigilance & RMP - Q4 2018 & Q4 2019

- SmPC

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Loss of/reduction in long-term efficacy due to persistent neutralising anti-drug antibodies	SmPC section 5.1 (Pharmacodynamic properties) states: Immunogenicity Overall, treatment -emergent anti- drug antibody response developed in 107 out of 809 (13%) patients treated with Fasenra at the recommended dosing regimen during the 48 to 56 week treatment period of the exacerbation trials. Most antibodies were neutralising and persistent. Anti -benralizumab antibodies were associated with increased clearance of benralizumab and increased blood eosinophil levels in patients with high anti-drug antibody titres compared to antibody negative patients; in rare cases, blood eosinophil levels returned to baseline levels. Based on current patient follow-up, no evidence of an association of anti- drug antibodies with efficacy or safety was observed	None

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Public_assessment_report/human/004433/WC500245333.pdf

Examples of Clinical Impact

Levels of Drug and Antidrug Antibodies Are Associated With Outcome of Interventions After Loss of Response to Infliximab or Adalimumab

Henit Yanai, Lev Lichtenstein, Amit Assa, Yoav Mazor, Batia Weiss, Arie Levine, Yulia Ron, Uri Kopylov, Yoram Bujanover, Yoram Rosenbach, Bella Ungar, Rami Eliakim, Yehuda Chowers, Raanan Shamir, Gerald Fraser, Iris Dotan and Shomron Ben-Horin

Clinical Gastroen

Neurology. 2007 Oct 2;69(14):1391-403. Epub 2007 Aug 29.

The incidence and significance of anti-natalizumab antibodies: results from AFFIR SENTINEL.

Calabresi PA[1], Giovannoni G, Confavreux C, Galetta SL, Havrdova E, Hutchinson M, Kappos L, Miller DH, O'Connor PW, Phillips JT, Rudick RA, Stuart WH, Lublin FD, Wajgt A, Weinstock-Guttman B, Wynn DR, Lynn F, Panzara MA; AFFIRM and SENTINEL Investiga

CONCLUSIONS: The incidence of persistent antibody positivity associated with natalizumab is 6%. Reduced clinical efficacy is apparent in persistently positive patients. Patients with a suboptimal clinical response or persistent infusion-related adverse events should be considered for antibody testing.

Neurology. 2013 Feb 6. [Epub ahead of print]

Fatal Neuroinflammation in a Case of Multiple Sclerosis with Anti-Natalizumab Antibodies.

Svenningsson A, Dring AM, Fogdell-Hahn A, Jones I, Engdahl E, Lundkvist M, Brännström T, Gilthorpe JD.

Mult Scler. 2013 Apr;19(5):593-600. doi: 10.1177/1352458512460604. Epub 2012 Sep 19.

Clinical relevance of serum natalizumab concentration and anti-natalizumab antibodies in multiple sclerosis.

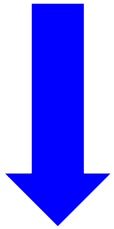
Vennegoor A[1], Rispens T, Strijbis EM, Seewann A, Uitdehaag BM, Balk LJ, Barkhof F, Polman CH, Wolbink G, Killestein J.

RESULTS: Antibodies were detected in 58% of the natalizumab-treated patients. All patients developed their antibodies before week 24. The large majority of these patients reverted to neutralizing antibody (NAb) negative status during follow-up. The presence of antibodies was inversely correlated with serum natalizumab concentration ($p<0.001$). Only high antibody titers are associated with very low or undetectable serum natalizumab concentration. Both high antibody titers and low serum natalizumab concentrations are associated with relapses and gadolinium-enhancing lesions on MRI.

Often the 'real impact' of ADA only becomes clear in a post-approval setting

Immunogenicity Data

ADA incidence, titer, onset, persistence, neutralizing capacity



ASSAYS

Evolved but still challenging

Drug Tolerance

METHODS: The immunogenicity assay drug tolerance, steady-state drug concentrations, and immunogenicity rates were reviewed for 26 BLA/NDA and 2 sBLA.

RESULTS: Many FDA approved biologics had higher steady-state drug concentrations than the drug tolerance of ADA assays, by 1.2- to 800-fold. Reported immunogenicity rates may be negatively impacted. Some sponsors triaged immunogenicity samples according to the drug tolerance, leaving some samples un-assayed or reporting them as inconclusive ADA; but these samples were interpreted as ADA- for calculating immunogenicity rates.

FDA Review : 2012
Products : 2005-2011

Pharmaceutical Research
December 2012, Volume 29, Issue 12, pp 3384–3392 | Cite as

A Survey of Applications of Biological Products for Drug Interference of Immunogenicity Assays

Authors Authors and affiliations

Yow-Ming C. Wang, Lanyan Fang, Lin Zhou, Jie Wang, Hae-Young Ahn

ADA Assays: Drug tolerance (DT) vs PK

- DT testing - Examine interference in signal from ADA positive sample (PC spiked into NHS) when excess drug is added

- Models risk of false negative test for ADA when excess drug binds ADA *in vivo* or *in vitro* and inhibits ADA detection in assays

- Evaluate drug PK – does on drug (trough) sampling risk false negative tests for ADA and prompt “off drug” sampling?

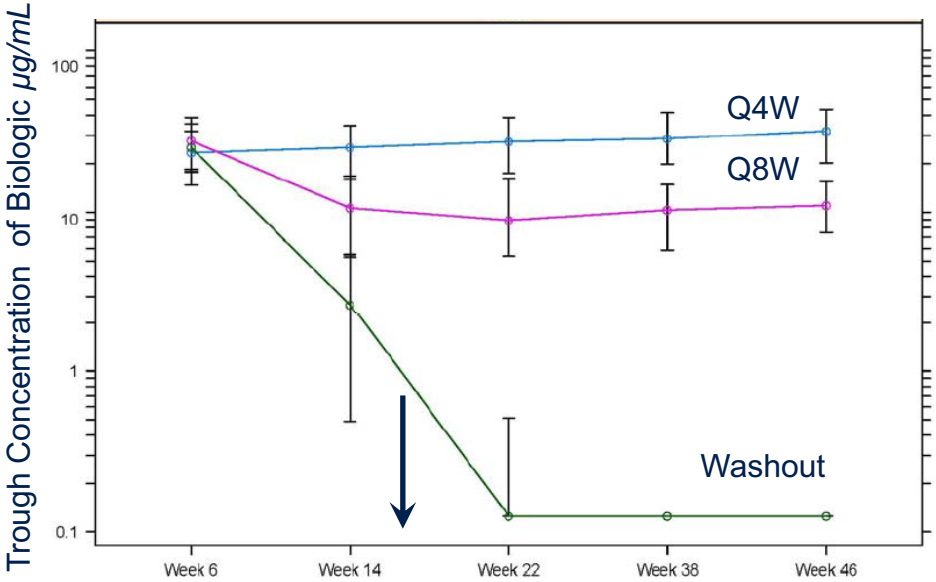
Example (mAb – chronic administration)

- Drug levels for Q4W, Q8W regimens and washout shown
- Final “off drug” sample: several t½ of drug washout so within DT limits

Drug tolerance of ADA Assays vs Population PK

Example : mAb – chronic administration

ECL assay with acid dissociation has better drug tolerance than ELISA but still ??



16 weeks after last dose of drug

Drug tolerance of LPC	ADA rates: Any +ve vs *Final Sample* *
ECL 5 µg/mL	6% vs *15%*
ELISA 1 µg/mL	4% vs *10%*

**Final "off drug" washout sample*

Benepali (SB4) versus Enbrel

ADA detected by ECL assay using SB4 (one-assay approach)

Phase 3 - RA patients (+ MTX)

Phase	ADA Incidence			
	SB4 Treatment Group		EU Enbrel® Treatment Group	
	N=299	(%)	N =297	(%)
Phase III (Wk 24)	2	**0.7**	39*	**13.2**
Wk 52	3	**1.0**	39*	**13.2**

Sampling: Baseline and Weeks 2, 4, 8, 12, 16 & 24;
Criteria : ADA +ve if 1 sample +ve at any time point; 1 patient NAb+ve *

There was a significant (p-value < 0.001) difference in overall ADA formation at week 24.

SB4 - lower aggregate content and HCP but did not explain the difference

Assay – Poor Drug tolerance

The drug tolerance level of ADA assay was close to the mean trough concentrations. There was a difference in the mean trough concentrations at weeks 4 and 8. This difference may have caused a bias in the ADA results.

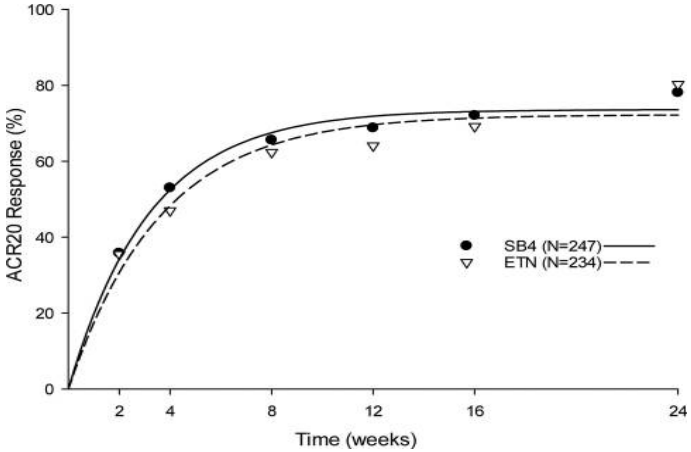
Table 31. Incidence of Overall ADA by Treatment Group by Ignoring Samples Taken at Weeks 4 and 8 (Safety Set, Study SB4-G31-RA)

Overall ADA Status	SB4 n/n' (%)	EU Enbrel n/n' (%)	*p*-value
24-week Overall ADA Incidence	0/299 (0.0)	2/296 (0.7)	0.2471
52-week Overall ADA Incidence	1/299 (0.3)	2/296 (0.7)	0.6225

SB4 no less immunogenic than Enbrel

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004007/WC500200380.pdf; Emery P et al Ann Rheum Dis. 2017; 76(1):51-57.

Benepali (SB4) versus Enbrel



Week 24 - ACR20 response rate in the per-protocol set was 78.1% for SB4 and 80.3% for ETN

SB4 no less immunogenic than Enbrel.
No impact on PK and safety.....

APPROVED - EMA

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004007/WC500200380.pdf; Emery P et al Ann Rheum Dis. 2017; 76(1):51-57.

EMA Immunogenicity Guideline (2017)

Drug Tolerance

The Applicant has to demonstrate that the drug tolerance of the assay exceeds the levels of the therapeutic protein in the samples for ADA testing. Due to technical limitations it may not be always possible to develop fully tolerant assays. If this occurs, the best possible assay should be employed and the approach taken should be properly justified.

EMA Immunogenicity Guideline (2017)

Neutralizing capacity of positives needs to be evaluated …..since this often correlates with diminished efficacy. Deviation ….needs a strong justification. In such cases, it is advisable to seek regulatory advice.

For a majority of products, 2 assay types largely dictated by mechanism of action

Cell-based bioassay	OR	Competitive ligand binding assay (CLBA)
Examples - IFN-beta, Rituximab		Example - Etanercept

Neutralizing Antibody Assays

Advantages	Disadvantages
Cell-Based	
Functional assay reflecting mechanism of action of therapeutic May correlate with clinical response	Can have complex protocol design Often variable. Affected by serum (matrix) effects and interfering factors Susceptible to interference by therapeutic Validation can be difficult e.g., cell-lines, reagents etc
Non-Cell-Based	
Rapid Simple assay design Relatively easy to use Does not require cell-lines Easy to develop and validate **Often highly sensitive**	Antigen labelling may alter antigen Susceptible to interference by therapeutic May not represent true functional read-out May not correlate with clinical response

Cell-based : Better insight on functional effects, favored by regulators

Assay choice: Cell-based - product MOA

If sufficient sensitivity, precision, robustness not achieved

Engage with regulators; Strong justification and data (transparency) – alternative approach may be acceptable

Example: Therapeutic antibody

- Humanised mAb; binds to receptor on certain cells with high affinity and induces their apoptosis in the presence of NK cells via ADCC
- Option: Cell-based assay
- Assays: reporter gene ADCC and LBA
- Assay sensitivity - LBA 35 fold more sensitive; better drug tolerance
- Approach - Comparative data for a clinical study using both assays

  LBA detected higher %age of nAb-positive samples vs cell-based

  Other evidence to show ADAs were directed against the CDR

  Justification - LBA selected for Phase III studies

EMA - Accepted .. …… BUT alignment with FDA?

Neutralizing Antibody Assays

Need for Nab Assays??

- Discussions – Strong opposition to removal of NAb assays
- Possible if strong justification for a waiver e.g., experience (GH, Insulin)
- Evidence from public domain (benefit to biosimilars)

BUT this is also applicable to other products

The immunogenic part of infliximab is the $F(ab')_2$, but measuring antibodies to the intact infliximab molecule is more clinically useful

Shomron Ben-Horin, Miri Yavzori, Lior Katz, Uri Kopylov, Orit Picard, Ella Fudim, Daniel Coscas, Simon Bar-Meir, Itamar Goldstein, Yehuda Chowers

Gut 2011;**60**:41–48. doi:10.1136/gut.2009.201533

Ann Rheum Dis. 2013 Jan;72(1):104-9. doi: 10.1136/annrheumdis-2012-201445. Epub 2012 Jul 3.

Adalimumab elicits a restricted anti-idiotypic antibody response in autoimmune patients resultin in functional neutralisation.

van Schouwenburg PA[1], van de Stadt LA, de Jong RN, van Buren EE, Kruithof S, de Groot E, Hart M, van Ham SM, Rispens T, Aarden L, Wolbink GJ, Wouters D.

Ann Rheum Dis. 2015 Jan;74(1):311-4. doi: 10.1136/annrheumdis-2014-206237. Epub 2014 Oct 23.

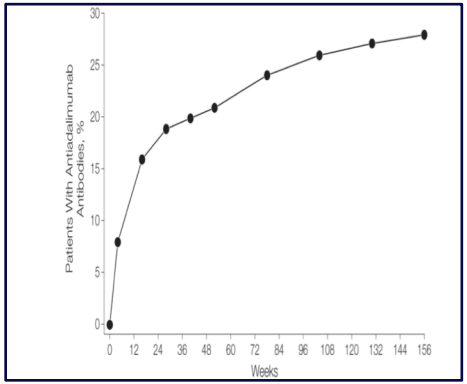
The antibody response against human and chimeric anti-TNF therapeutic antibodies primarily targets the TNF binding region.

van Schie KA[1], Hart MH[1], de Groot ER[1], Kruithof S[1], Aarden LA[1], Wolbink GJ[2], Rispens T[1].

Antibodies and Clinical impact

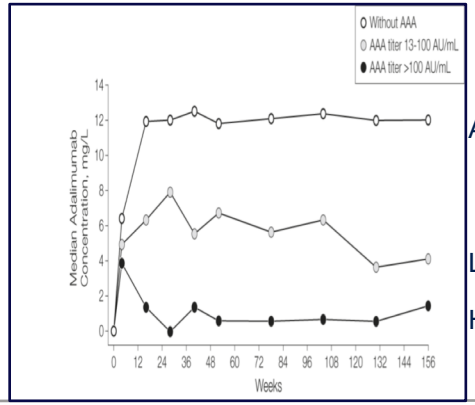
RA patients treated with Adalimumab over 3 years

A



28%

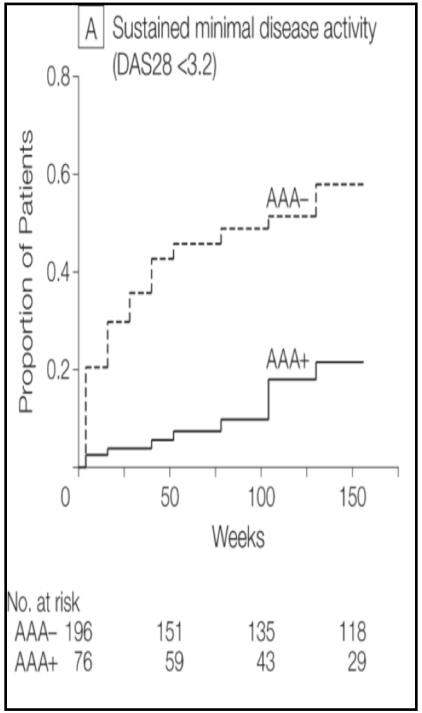
B



Ab -ve

Low Ab

High Ab



Abs develop within 24 weeks

diminish levels of therapeutic

compromise efficacy

Bartelds et al : **Development of Antidrug Antibodies Against Adalimumab and Association With Disease Activity and Treatment Failure During Long-term Follow-up** JAMA. 2011;305(14):1460-1468.

ABP 501* vs Humira

Table 29. Summary of Binding and Neutralizing ADAs Following Repeat Dosing in Study 262 and Study 263

	Rheumatoid Arthritis Study 262		Plaque Psoriasis Study 263				
			Through Week 16		Week 16 to EOS		
	ABP 501 40 mg (n=264)	US-ADA 40 mg (n=262)	ABP 501 40 mg (n=174)	US-ADA 40 mg (n=173)	ABP 501/ ABP 501 40 mg (n=152)	EU-ADA/ EU-ADA 40 mg (n=79)	EU-ADA/ ABP 501 40 mg (n=77)
Binding ADA-positive, n (%)	101 (38)	100 (38)	96 (55)	110 (64)	104 (68)	59 (75)	56 (73)
Neutralizing ADA-positive, n (%)	24 (9)	29 (11)	17 (10)	24 (14)	21 (14)	16 (20)	19 (25)

Source: FDA analysis of data from Amgen 351(k) BLA submission
US-ADA: US-licensed Humira; EU-ADA: EU-approved Humira; EOS: end of study

*Amgevita

https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/arthritisadvisorycommittee/ucm510293.pdf

Clinical Impact of ADA

ADA incidence: Similar for the reference and biosimilar ABP501

For both products:

- ADA-positive patients had a lower exposure (troughs)
- ADA-positive patients had inferior efficacy
- Hypersensitivity/injection-site reactions were similar regardless of ADA status
- NAbs did not have a statistically significant differential impact on efficacy between the two products

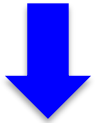
- Similar situation seen with Remicade and Remsima
- Relevance of NAb Assay ????

Immunogenicity Testing

Any possibility of waiving of NAb assays for new products?

Discuss with regulatory agency

Case-by-Case



Product need, favourable benefit risk profile, NAb assay data, in vivo PK, PD data

EMA Immunogenicity Guideline (2017)

Biosimilars : Comparative immunogenicity needs to be demonstrated pre-licensing

- Head-to-Head studies
  - Sensitive, homogeneous and clinically relevant patient population (ideally naïve). Extrapolation perspective
  - Suitable design, size – allows conclusion on ADA and clinical impact
  - Same sampling points (baseline, sequential etc) based on product PK, assay drug tolerance

- Sampling for ADA (& for drug) in pivotal PK, PD, safety & efficacy studies
- Study duration – product based; in chronic treatment (1 year normally)
- Consider risk (previous experience, any potentially immunogenic structures, patient population)

Comparative Immunogenicity : Biosimilars

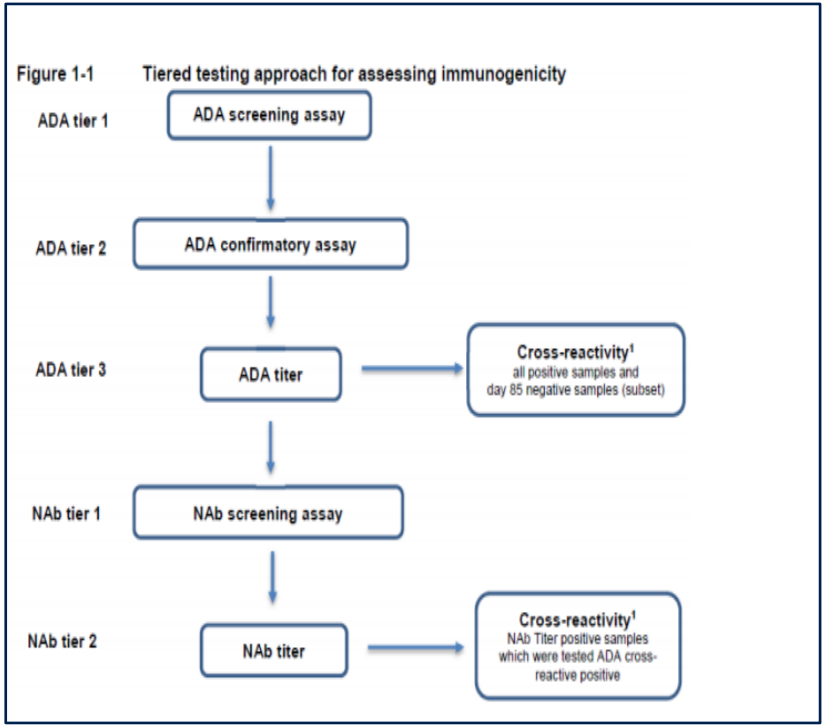
- State-of-art assays using administered therapeutic product (true immunogenicity)
- Options –
  - 2 assays with similar sensitivity and specificity and no bias in recognition,
  - single assay using 'biosimilar' for both arms (relative) with confirmatory using both products. Variability minimised BUT risk of under-estimating RMP immunogenicity

- Expectation –
  - Antigenic equivalence shown and assay suitable (antibody control/s)
  - Clinical sample data showing concordance (excess drug – equivalence)

In the EU, both approaches accepted for biosimilars approved

Biosimilar Infliximab – One Assay

- Initially 2 screening assays (Phase 1)
- Cross-validation of assays – clinical samples tested; good cross-reactivity (equivalence)
- Slight differences in assays noted w.r.t sensitivity etc
- Phase III – 1 assay (biosimilar)
- Similar approach taken for Nabs



Accepted-EMA

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004647/WC500249649.pdf

Comparative Immunogenicity: Biosimilars

- Similar antibody incidence, titres, neutralization, kinetics of development
- If differences identified, an understanding of the root cause needed e.g., impurities, aggregates etc
  - Excess immunogenicity not compatible with biosimilarity BUT
  - Lower immunogenicity does not preclude biosimilarity. Justification required. Data assessed in context of totality of evidence
- The consequences of ADA also must be compared….Any impact on PK,PD, efficacy, safety etc ?
- **Expectation** - Clinical impact not worse than the RMP
- Post-approval surveillance of immunogenicity is a key requirement for all biosimilars e.g., monitoring of any immune-mediated adverse effects.
- Special studies in high risk situations e.g., where serious but rare effects (anaphylaxis) known with reference product.

Biosimilar MAbs – Two Antigen Assay

- Initial testing used a single antigen (reference product) → no difference seen
- Assay using the biosimilar as antigen developed → no difference seen, including ADA titers.
-

Indication	Remsima	Remicade (reference)
AS	37.5%	36.1%
RA	55.6%	54.3%

- Cross testing of sera with both assays → good concordance → evidence for similar immunogenicity
- Similar impact on clinical efficacy and safety

APPROVED

ABP 501 vs Humira

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APPROVED

https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/arthritisadvisorycommittee/ucm510293.pdf

Biosimilar Infliximab – One Assay

Phase III – Randomised, Double blind study to assess efficacy and safety of Zessly and Infliximab in combination with Methotrexate in patients with moderate to severe RA who have had an inadequate response to methotrexate

A similar proportion of patients with ADAs, similar onset times and respective titers of ADAs were observed for the Zessly and EU-authorized Remicade arms. The proportions of patients with ADAs after dose escalation were also similar between treatment arms. The proportions of patients with NAbs in ADA-positive patients were similar between treatment arms.

The development of ADAs lead to lower average C_{trough} and C_{max} concentrations in ADA-positive patients for both Zessly and EU-authorized Remicade. The frequency of ADA and NAbs was generally slightly lower in the Zessly arm.

In-line with historical data on Remicade, in all treatment groups up to week 54, the response rates were higher in patients that were ADA negative compared to those that were ADA/NAb positive.

These results demonstrate equivalence in clinical efficacy between the proposed biosimilar Zessly (Zessly) and the reference product Remicade (EU-authorized Remicade).

Similar safety profile too!

APPROVED - EMA

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004647/WC500249649.pdf

EMA Immunogenicity Guideline (2017)

Recommends inclusion of :

- an integrated summary of immunogenicity in the application, including a risk assessment to support the selected immunogenicity program.
- in chapter 2.7.2.4 Special Studies or, if more detailed, in chapter 5.3.5.3 of the CTD.
- concise and contain links to the appropriate chapters of the application.
- This summary with risk assessment can evolve through the lifecycle of the product and support application at various steps of product development

Immunogenicity : Some Considerations

- Modern assays, evolve over time → validated assays → reports
  - Clear description (incl amendments), SOPs
  - Clear description – approach for outliers and calculation of CP
  - MRD – how determined
  - Titre – how defined
- Nab Assays : Cell-based, information on optimal therapeutic dose, dose-response curve
- Drug Tolerance : Cover plausible levels of therapeutic (not just 1)
- Sampling for ADA, therapeutic
- Same +ve control(s) as assay evolves; information, COA, life-cycle perspective. For Nab assay, +ve control with neutralization activity
- Data : Need for harmonized terminologies and reporting

Summary

Conclusion

The AAPS Journal, Vol. 19, No. 3, May 2017 (© 2017)
DOI: 10.1208/s12248-017-0059-7

Commentary

A Proposal to Redefine Clinical Immunogenicity Assessment

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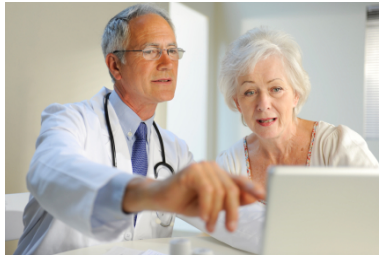

An immunogenicity testing approach based on
- scientific knowledge and risk considerations with sufficient data which
- informs the prescriber of product immunogenicity and potential outcomes for clinical decision-making

Seek ‘regulatory opinion’ where possible…….

Acknowledgement

- Biosimilar Medicines Working Party members (Immunogenicity Guideline Drafting Group) – Pekka Kurki, Robin Thorpe
- Clinical assessors – Andrew Exley, Marie-Christine Bielsky

Thank You!