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Tailored immunogenicity program – why?

Disclosures

- Received compansation for speaking/advising and/or research support from
  - Biogen
  - Merck
  - Roche
  - Novartis
  - Genzyme

Summary of the immunogenicity program

Analysis of risk factors

1. Previous experience of the product/product class
    a. does the product have an endogenous counterpart
    b. do animal models provide useful data of potential consequences of immunogenicity (e.g. elimination of an endogenous protein)
    c. are there known antigenic sites of the molecule
    d. attempts to reduce the immunogenicity of the product before and during clinical trials

2. Physicochemical and structural aspects
    a. Are there potentially immunogenic structures, e.g. sequences that are foreign to human
    b. Expression construct and the posttranslational profile e.g. non-human glycosylation patterns/glycans
    c. Stability and impurities (e.g. presence of aggregates (as visible or sub-visible particles)
    d. Formulation and packaging, e.g. potential impurities and leachables
3. Does the route and/or the mode of administration raise concerns
4. Patient- and disease-related factors
    a. State of the immunological tolerance
        i. prone to autoimmune reactions
        ii. lack of immunological tolerance, e.g. defects in genes coding for endogenous proteins
        iii. concomitant immunomodulative therapy
    b. Pre-existing immunity
        i. "natural" antibodies
        ii. cross-reactive antibodies, e.g. due to previous therapy with related substances

The risk-based immunogenicity program

5. Assay strategy
    a. Rational for the choice of assays
        i. screening and confirmation
        ii. neutralizing
        iii. other, e.g. immunoglobulin class, sub-class
    b. Specificity and sensitivity of the selected assays in the context of the particular product
        i. selection of the positive control(s)
        ii. determination of the threshold for ADA-positivity
    c. Drug tolerance of the assay at therapeutic concentrations

6. Approach to immunogenicity in clinical trials
    a. Sampling for immunogenicity testing
    b. Justification for the length of the follow up
        i. on-treatment
        ii. off-treatment, post-exposure
    c. Pharmacokinetics
    d. Pharmacodynamics, efficacy and safety trials
        i. how the program aims to reveal the incidence, persistence and clinical significance of potential ADAs
        ii. antigen tolerance of the ADA assay and the trough concentrations
        iii. loss of efficacy, hypersensitivity, autoimmunity
            1. definitions and symptom complexes[1]
            2. analysis of clinical correlations of ADAs
7. Impact on the risk assessment on the immunogenicity program

Immunogenicity results

8. Immunogenicity in clinical trials (relative immunogenicity in case of manufacturing changes and biosimilars)
    a. (Relative) incidence of ADAs, including neutralising ADAs
    b. (Relative) titres and persistence over time
    c. Further characterisation if appropriate, e.g. immunoglobulin classes, cross-reactivity with related therapeutic or endogenous proteins
    d. Impact of ADAs on pharmacokinetics
    e. Impact of ADAs on pharmacodynamics, efficacy and safety
    f. Impact of pre-existing antibodies on pharmacokinetics, safety and efficacy

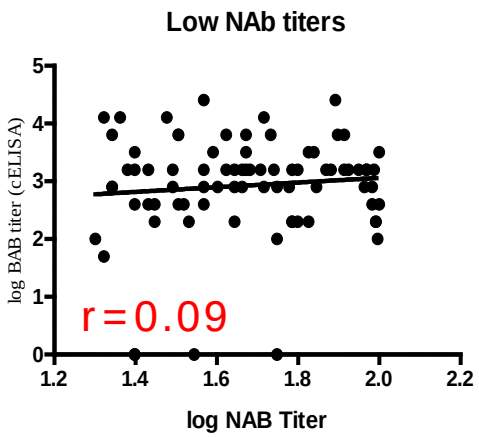
Conclusions on the risk(s) of immunogenicity

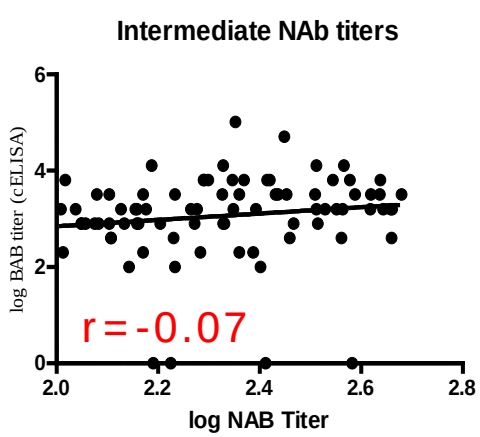
9. Impact of the immunogenicity on the benefit/risk
10. Tools to manage the risk
    a. Identification of risk groups
    b. Is there a safe level or type of immunogenicity
    c. Pre-medication
    d. De-immunisation
    e. Risk detection and mitigation tools
11. How to link adverse events to immunogenicity post-marketing

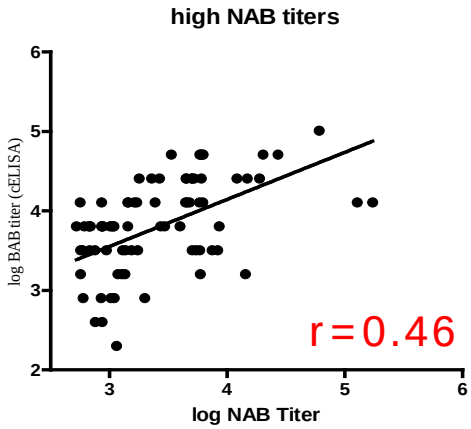
Overview

Drug	Indication	Type of product	ADA frequency	ADA consequences
IFNb	Multiple Sclerosis	Cytokine, native protein	1-30%	Breakthrough disease – alternative Rx
F VIII	haemophilia	Coagulation factor, native protein	20-30%	Breakthrough disease – Removal of ADA
Epo	anaemia	Enzyme, native protein	Eprex only	PRCA
Adalimumab	RA, IBD	Human mAb, anti-TNF	10-25%	Breakthrough disease – alternative Rx
Infliximab	RA, IBD	Chimeric mAb, anti-TNF	10-50%	Mostly IRA
Natalizumab	Multiple Sclerosis	Humanized mAb, anti VLA-4	5%	IRA, breakthrough disease – alternat. RX
Alemtuzumab	MS	Humanized mAb, anti-CD52	93%	IRA?

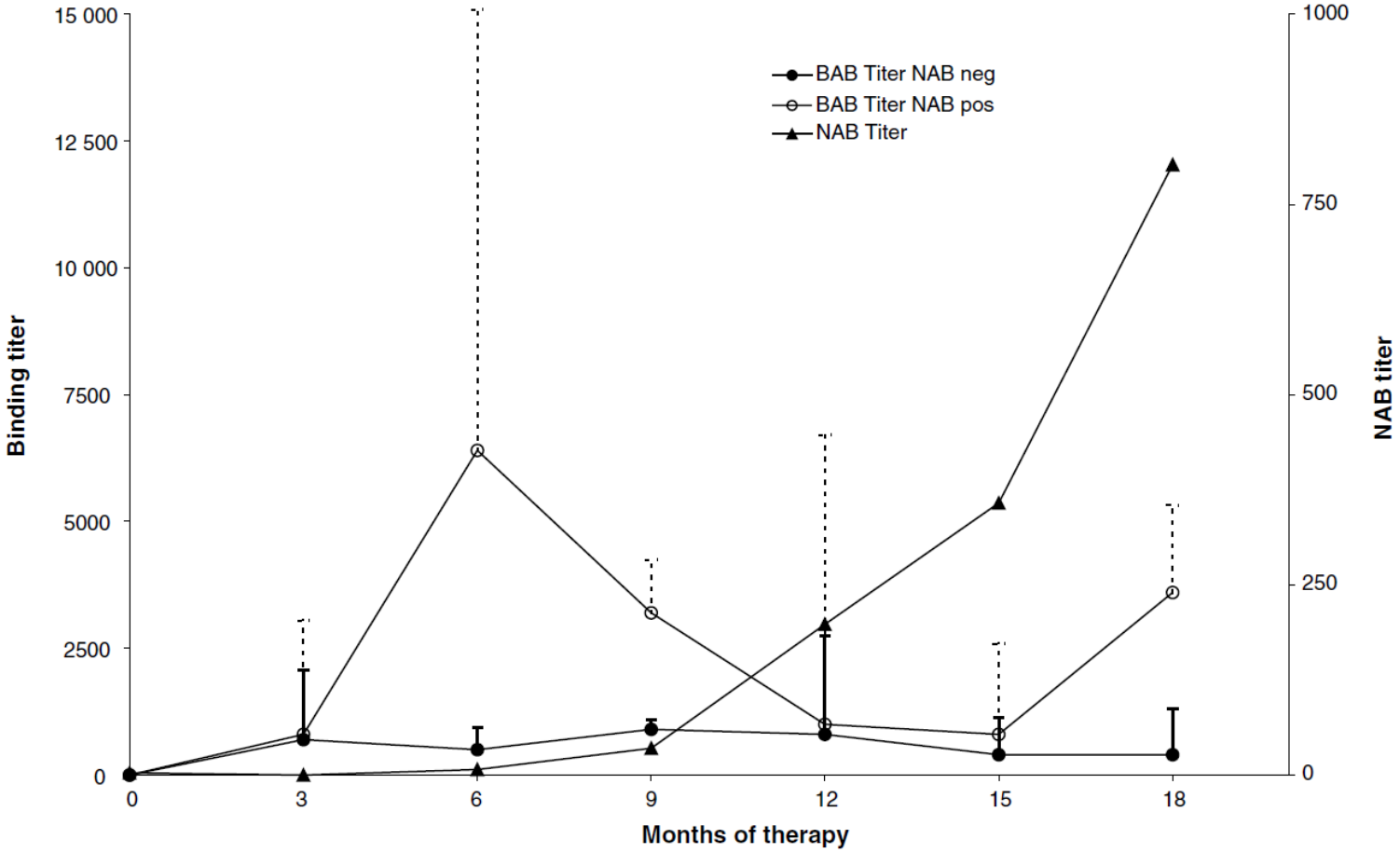
BAB and NAB correlation depending on NAB titre





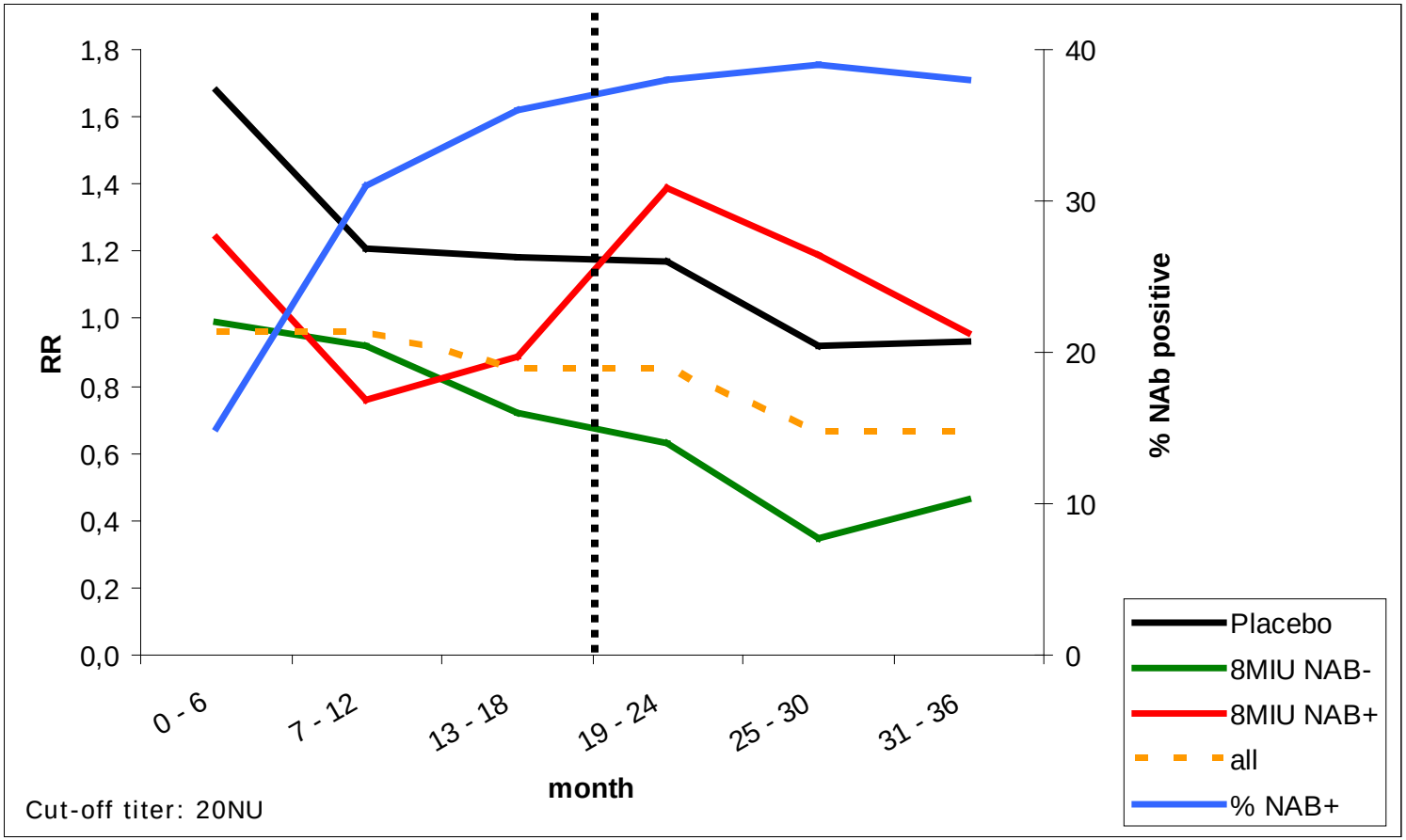


IFN BAB and NAB kinetics



European Journal of Neurology 2003, 10: 1–2

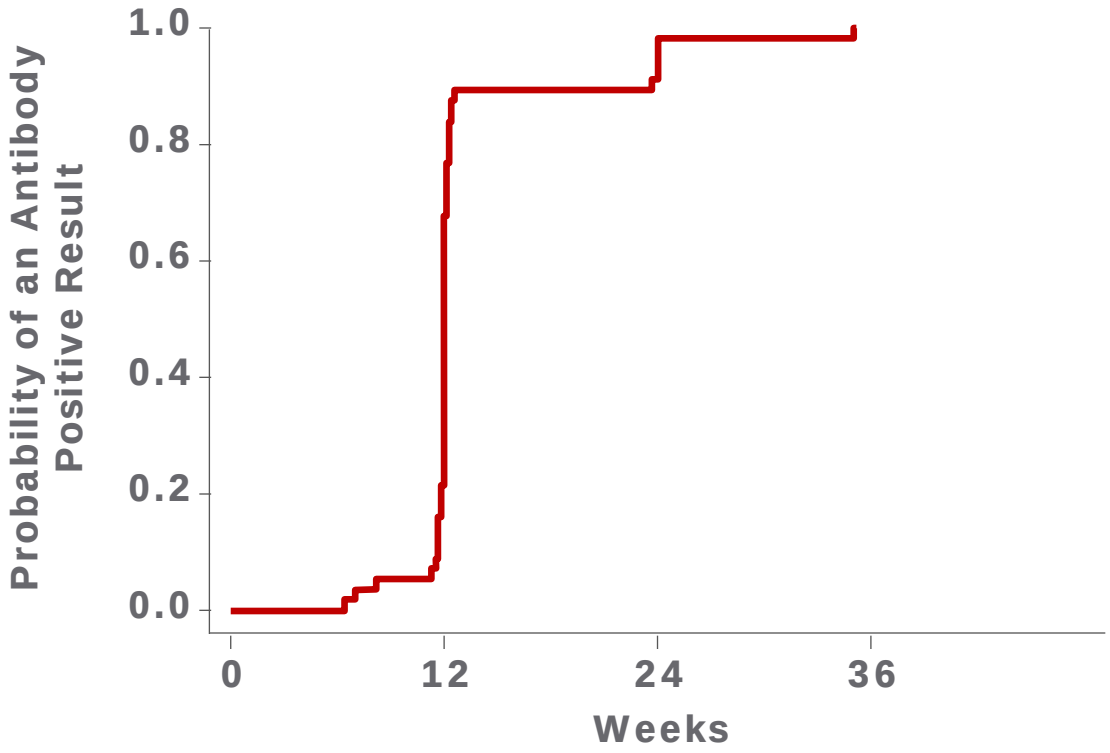
NAB timeline (Betaferon trial)



IFNB study group
Neurology 1996;47:889-894

Time of First Positive Result

In Patients Who Developed Any Antibodies

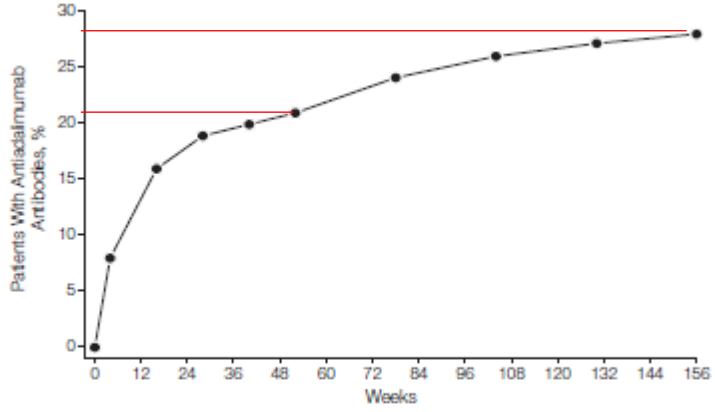


Number of Subjects at Risk

56	18	1	0

Adalimumab Abs

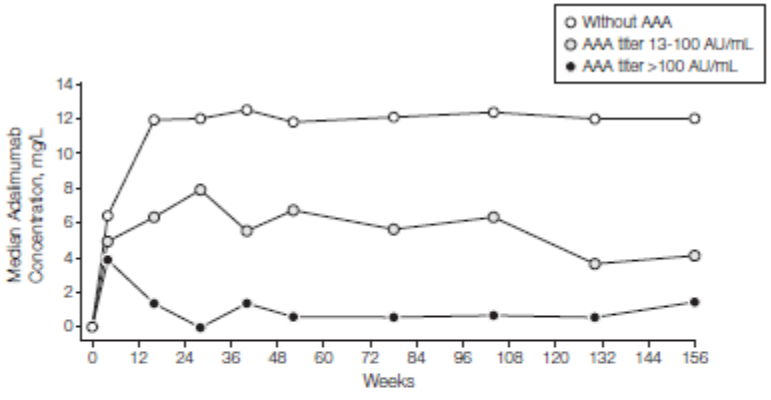
Figure 1. Percentage of Antiadalimumab Development Over Time



Week	0	4	16	28	40	52	78	104	130	156
No. of patients	272	261	247	228	201	192	175	156	137	118

Number of patients with available serum samples are shown.

Figure 2. Median Adalimumab Concentrations Over Time



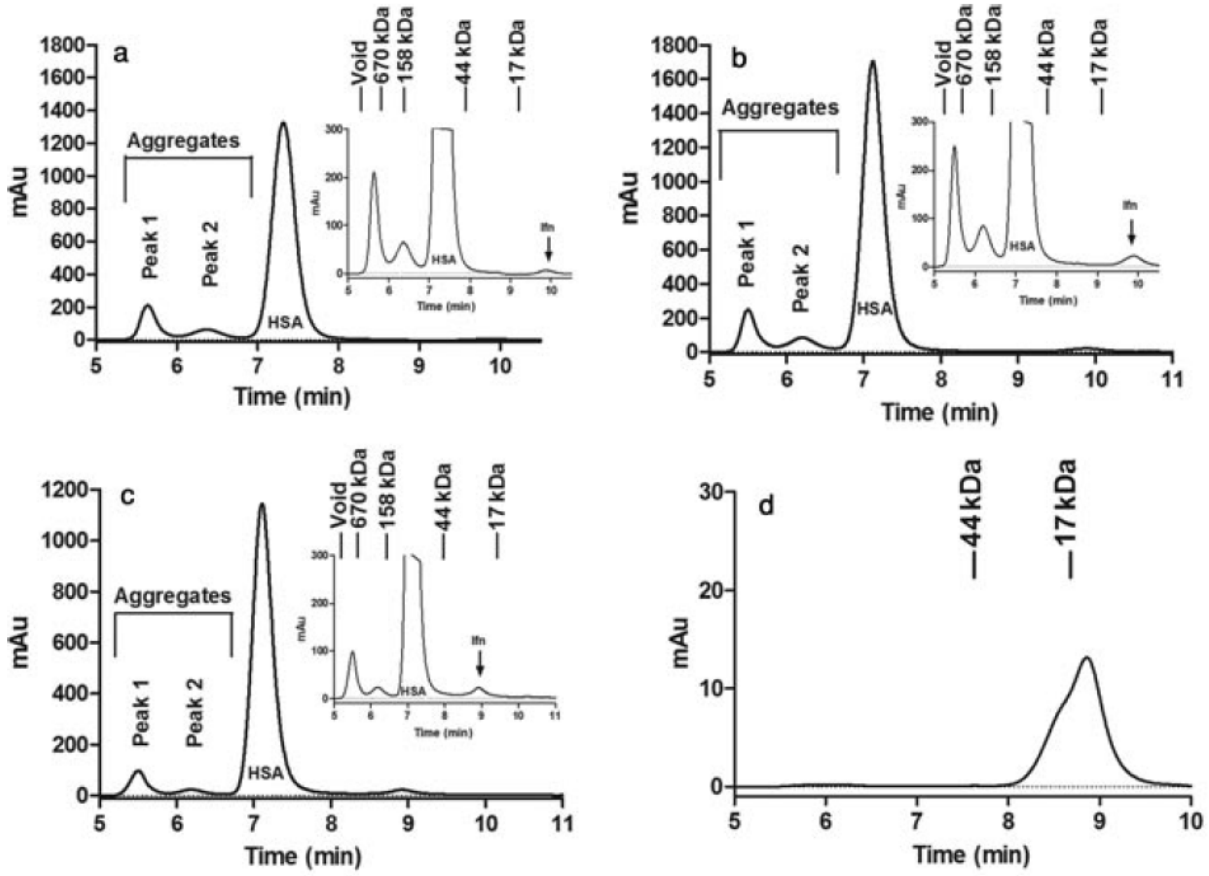
Week	0	4	16	28	40	52	78	104	130	156
No. of patients										
Without AAA	196	187	177	164	145	139	131	118	107	93
AAA 13-100 AU/ml	45	43	42	37	34	34	28	24	19	17
AAA >100 AU/ml	31	31	28	27	22	19	16	14	11	8

Median adalimumab concentrations (mg/L) per time point are shown for patients without antiadalimumab antibodies (AAA), with low AAA (13-100 AU/mL), and high antiadalimumab titers (>100 AU/mL). Patients who were AAA-negative had significantly higher adalimumab concentrations compared with patients with low AAA ($P<.001$) and high antibody titers ($P<.001$), with regression coefficients of −4.5 (95% confidence interval, −6.0 to −2.9) and −7.1 (95% confidence interval, −8.4 to −5.8), respectively (analysis by generalized estimating equation). The interquartile ranges (25th-75th percentiles) for the adalimumab concentrations ranged from 4.3-8.9 mg/L to 7.5-17.5 mg/L for the AAA-negative patients; from 3.4-7.1 mg/L to 2.2-11.7 mg/L for patients with low AAA; and from 0.0-2.7 mg/L to 0.01-11.2 mg/L for patients with high AAA titers.

Avonex NAB story

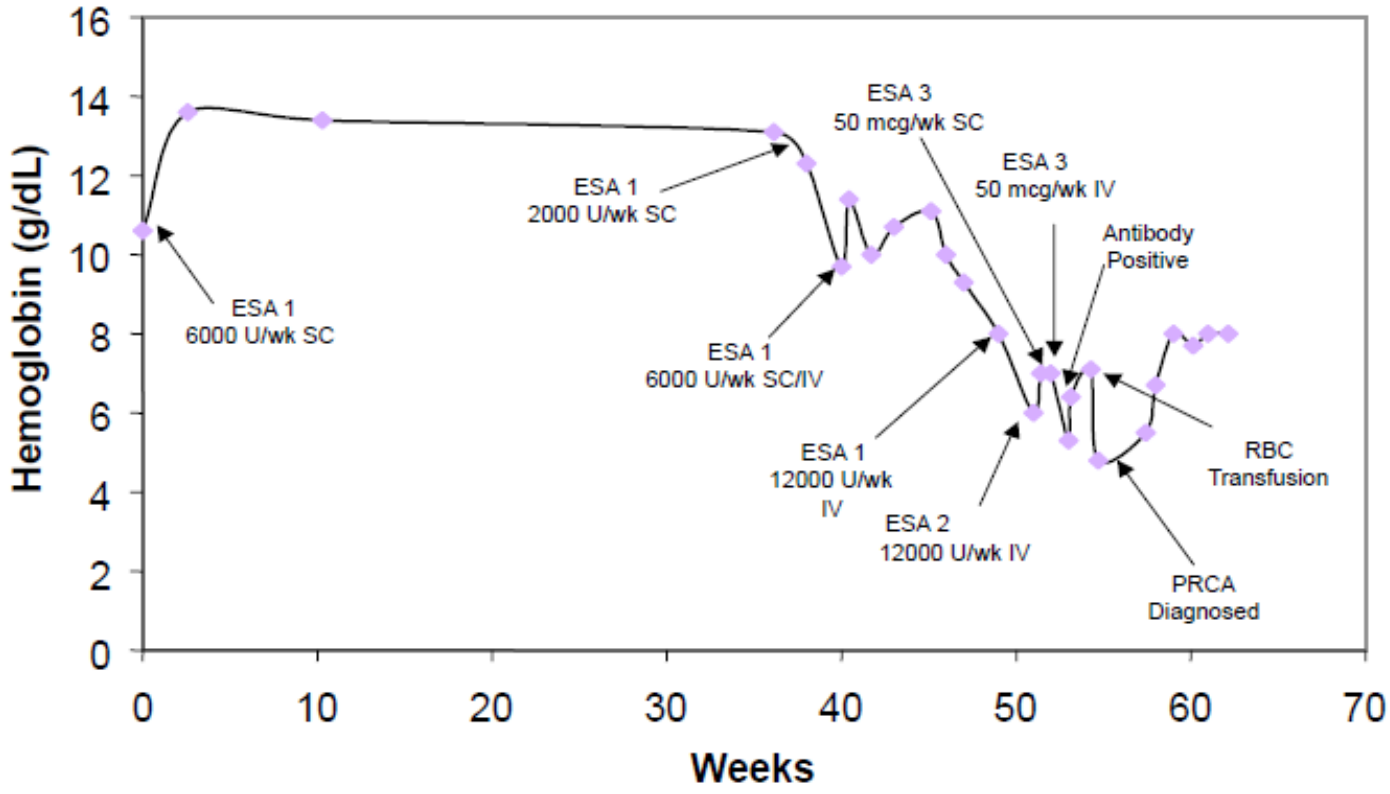
- Change of manufacturing
- Removal of HSA
- Reduction of
  - Aggregation
  - Oxidation
- NAB: 22% $\rightarrow$ 2-5%

Drug aggregates and NABs



Journal of pharmaceutical sciences, vol. 102, no. 3, march 2013

Epo antibodies



Adapted from *JASN* 2002;13:2381-2383

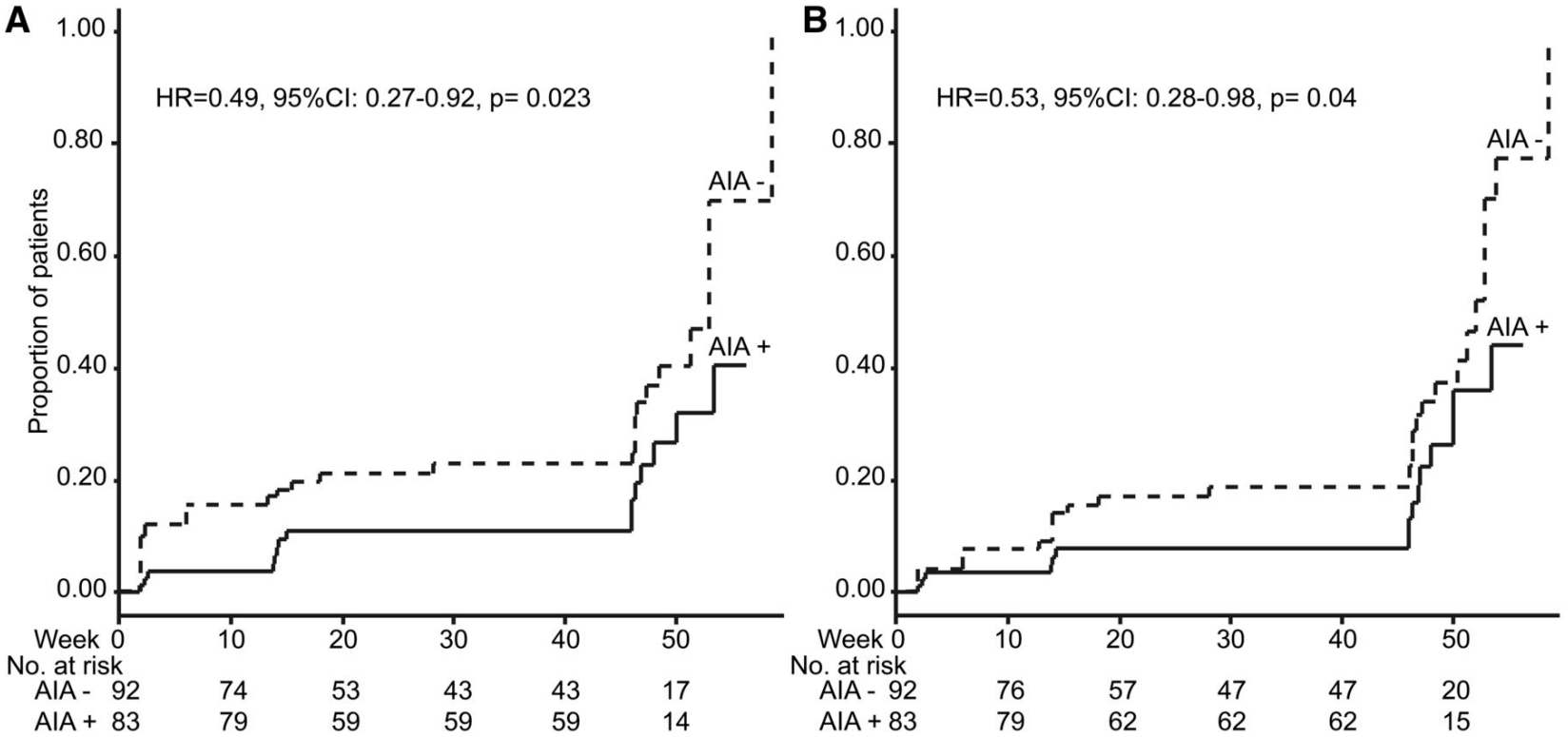
The Eprex story

The **increase in reported cases** coincides with the **removal of human serum albumin from the ex-US formulation of epoetin alfa**, in order to comply with new regulations from the European regulatory authorities.
It has been proposed that the **new formulation is less stable, allowing aggregates** of erythropoietin molecules to form, which increases the probability of antibody formation

Nephrol. Dial. Transplant. (2003) 18 (suppl 8): viii37-viii41. doi: 10.1093/ndt/gfg1091

ABIRISK

Sustained minimal disease activity and sustained remission.Sustained minimal disease activity (A) and sustained remission (B) in patients classified according to anti-infliximab status during the 52-week follow-up.



Sophine B. Krintel et al. Rheumatology 2013;52:1245-1253

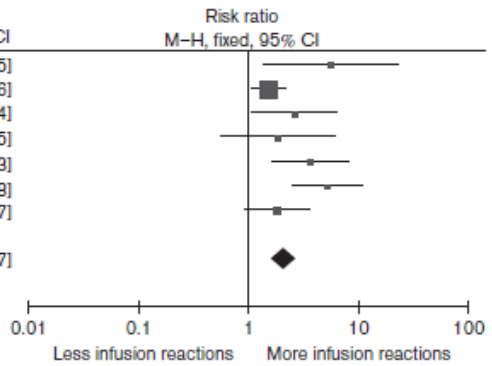
Clinical consequences of anti-Infliximab Abs in IBD

Fig. 3

Study or subgroup	ATI +ve Events	ATI +ve Total	ATI –ve Events	ATI –ve Total	Weight	Risk ratio M-H, fixed, 95% CI
Farrell *et al.* [18]	10	25	2	28	3.5%	5.60 [1.35, 23.15]
Hanauer *et al.* [11]	29	80	71	297	56.4%	1.52 [1.06, 2.16]
Maser *et al.* [4]	11	22	5	26	8.6%	2.60 [1.07, 6.34]
Miele *et al.* [12]	4	12	4	22	5.3%	1.83 [0.56, 6.05]
Rutgeerts *et al.* [14]	5	14	21	215	4.8%	3.66 [1.62, 8.23]
Rutgeerts *et al.* [14]	6	12	17	176	4.1%	5.18 [2.51, 10.68]
Sands *et al.* [15]	13	44	13	80	17.3%	1.82 [0.93, 3.57]
Total (95% CI)		209		844	100.0%	2.07 [1.61, 2.67]
Total events	78		133			

Heterogenity: $\chi^2 = 13.32$, $d.f. = 6$ ($P = 0.04$); $I^2 = 55\%$

Test for overall effect: $Z = 5.67$ ($P < 0.00001$)



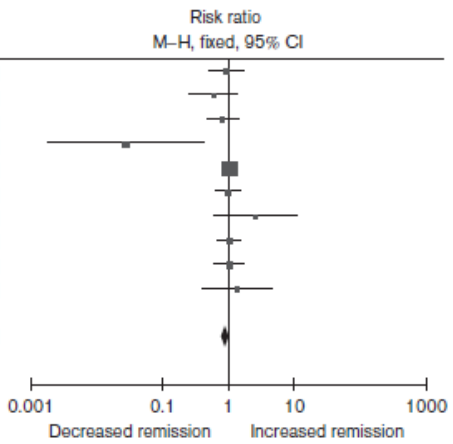
Rates of infusion reactions.

Fig. 4

Study or subgroup	Positive ATI Events	Positive ATI Total	Negative ATI Events	Negative ATI Total	Weight	Risk ratio M-H, fixed, 95% CI
Ainsworth *et al.* [20]	10	18	9	15	4.9%	0.93 [0.52,1.66]
Candon *et al.* [21]	3	6	11	13	3.5%	0.59 [0.26,1.36]
Colombel *et al.* [9]	8	14	12	17	5.4%	0.81 [0.47, 1.40]
Farrell *et al.* [18]	0	25	30	43	11.3%	0.03 [0.00, 0.43]
Hanauer *et al.* [11]	62	80	223	297	47.0%	1.03 [0.90, 1.18]
Maser *et al.* [4]	14	22	17	26	7.7%	0.97 [0.64, 1.48]
Rutgeerts *et al.* [14]	3	14	3	36	0.8%	2.57 [0.59, 11.26]
Rutgeerts *et al.* [14]	11	19	45	79	8.7%	1.02 [0.66, 1.56]
Sands *et al.* [15]	14	44	25	80	8.8%	1.02 [0.59, 1.75]
Seow *et al.* [3]	8	44	3	22	2.0%	1.33 [0.39, 4.54]
Total (95% CI)		286		628	100.0%	0.90 [0.79, 1.02]
Total events	133		378			

Heterogeneity: $\chi^2 = 14.32$, $d.f. = 9$ ($P = 0.11$); $I^2 = 37\%$

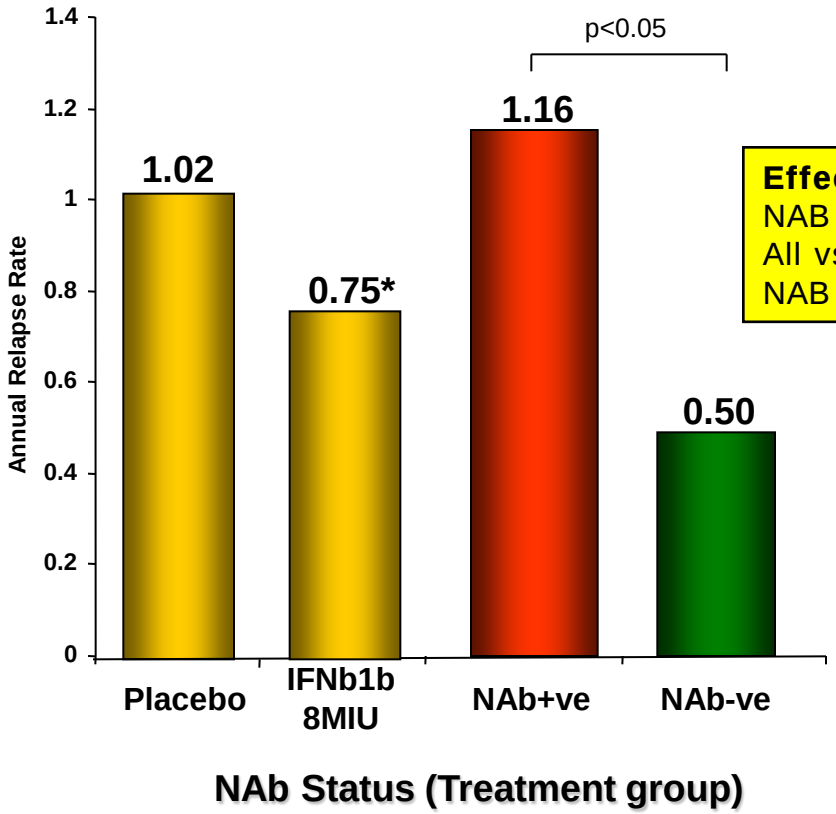
Test for overall effect: $Z = 1.64$ ($P = 0.10$)



Rates of clinical remission. ATI, anti-infliximab antibodies.

European Journal of Gastroenterology & Hepatology 2012, 24:1078–1085

IFNβ - Clinical Impact



Effect size year 3	RR
NAB pos vs Pl	+17%
All vs Pl	- 28%
NAB neg vs Pl	- 57%

*Neurology 1996;47:889-894; *approximately*

F VIII ADA treatment-strategies NAB incidence 20-30%

- Eradication of inhibitors
  - Spontaneous remission
  - **Immune tolerance therapy**
  - Immunosuppression therapy

- Management of bleeds
  - Low responding inhibitors
    - Increased dosage of factor VIII
  - High responding inhibitors
    - Bypassing agents
      - Recombinant factor VIIa (NovoSeven®, Novo Nordisk)
      - Plasma derived activated prothrombin complex concentrate (FEIBA®, Baxter)
    - Recombinant porcine FVIII
      - Studies in progress

HINABS II – NAB outcomes

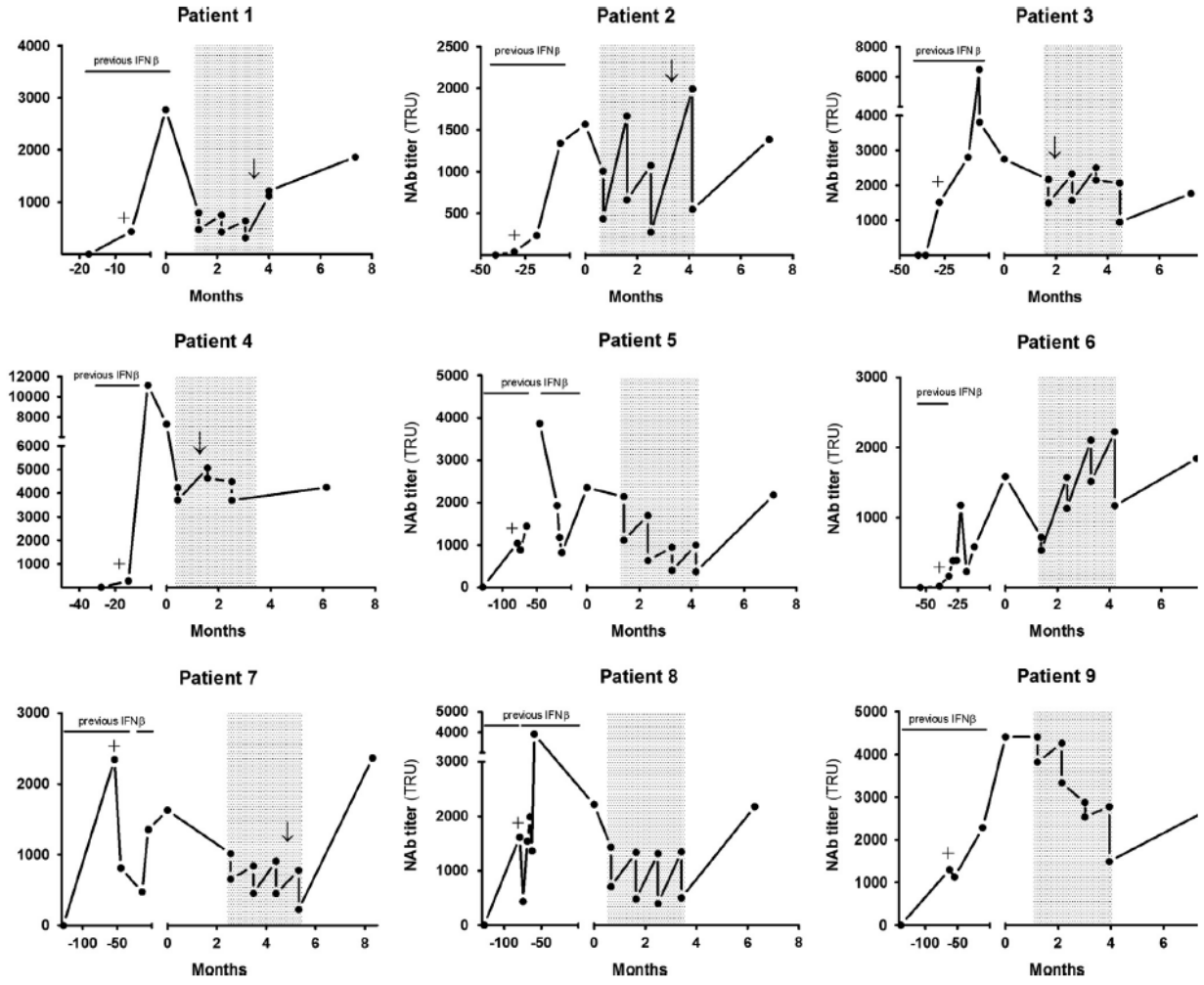


Fig. 3 Individual NAb titer development. NAb, neutralizing antibody; TRU, 10-fold reduction unit; IFNβ, interferon-beta; +, first NAb positive test; ↓, adverse event.

Multiple Sclerosis and Related Disorders (2014) 3, 220–226

Summary

- ADA frequencies depends:
  - drug properties
  - underlying disease/treatment
  - assay sensitivity
  - time on treatment
  - patients genetic makeup
- There is no biodrug with zero immunogenicity
- Severity of clinical consequences depends:
  - type of response (hypersensitivity – neutralization)
  - the severity of the disease
  - drug‘s effectivness and MOA
  - redundancy of the target

Thanks.....

to my team and for your attention

ABIRISK PROJECT

April 1st 2016 - Innsbruck Medical University, Innsbruck - Austria

FIRST ABIRISK DRUG IMMUNOGENICITY CONFERENCE

Free registration!

Backup

Frequency of NAB

Exogenous factors

Preparation	Patients tested for NAb	NAb positive N (%)	High titer N (%)
IFNb-1b	239	74 (31%)	43 (18%)
IFNb-1a i.m.	202	11 (5%)	9 (4%)
IFNβ-1a s.c.	405	118 (29%)	83 (20%)
Total	846	203 (24%)	**135 (16%)**
PEG-IFNb-1a		<1%	

χ^2: $p < 0.0001$

Multiple Sclerosis 2006; 12: 731-737