16° ΠΑΝΕΛΛΗΝΙΟ ΣΥΝΕΔΡΙΟ ΕΠΕΜΥ
με διεθνή συμμετοχή
SCIENTIFIC CONFERENCE
ON THE MUSCULOSKELETAL HEALTH
3-6 ΟΚΤΩΒΡΙΟΥ 2024 Ξενοδοχείο Du Lac, ΙΩΑΝΝΙΝΑ

Αντιφαρμακευτικά αντισώματα: Μύθοι και Αλήθειες

Θεραπεύοντας ΡΑ και ΑΣ

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Ρευματολόγος

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ΠΓΝΛάρισας

Σύγκρουση συμφερόντων

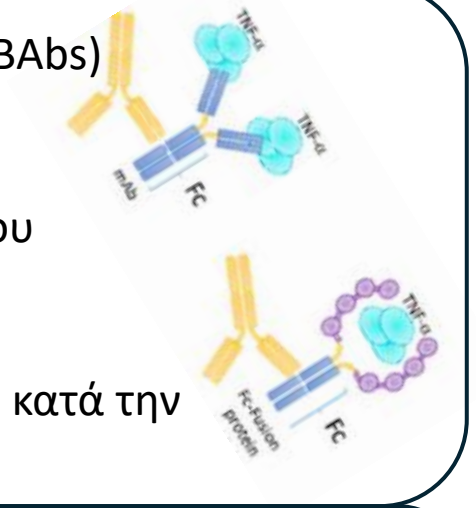
Καμία για τη συγκεκριμένη παρουσίαση

Αντιφαρμακευτικά αντισώματα - Anti-drug antibodies (ADAbs)

Τα βιολογικά φάρμακα, όπως κάθε ξένη πρωτεΐνη, μπορούν να ενεργοποιήσουν την παραγωγή αντισωμάτων και τους μηχανισμούς της κυτταρικής ανοσίας

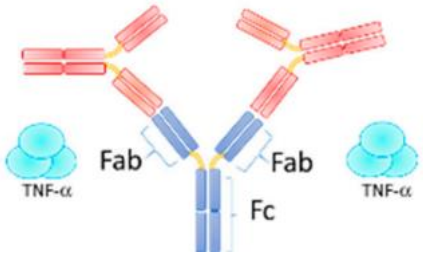
Μη εξουδετερωτικά (ή δεσμευτικά αντισώματα, Binding Antibodies, BAbs)

- Δεν παρεμποδίζουν τη σύνδεση του φαρμάκου με τον TNF
- Δεσμεύονται με Fc- και μειώνουν έμμεσα το επίπεδο του φαρμάκου αυξάνοντας την κάθαρση του φαρμάκου μέσω σχηματισμού ανοσοσυμπλεγμάτων
- Μπορεί να προκαλέσουν ανεπιθύμητες ενέργειες π.χ. αντιδράσεις κατά την έγχυση



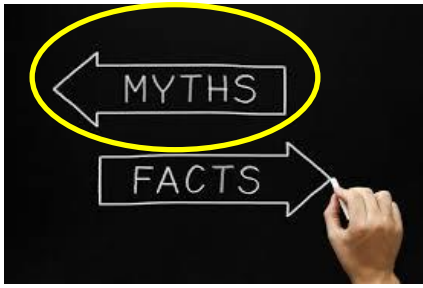
Εξουδετερωτικά (Neutralizing Antibodies, Nabs)

- Παρεμβαίνουν στην ικανότητα του φαρμάκου να δεσμεύεται στον στόχο του
- Μπορεί να έχει άμεσο αρνητικό αντίκτυπο στο λειτουργικό επίπεδο φαρμάκου

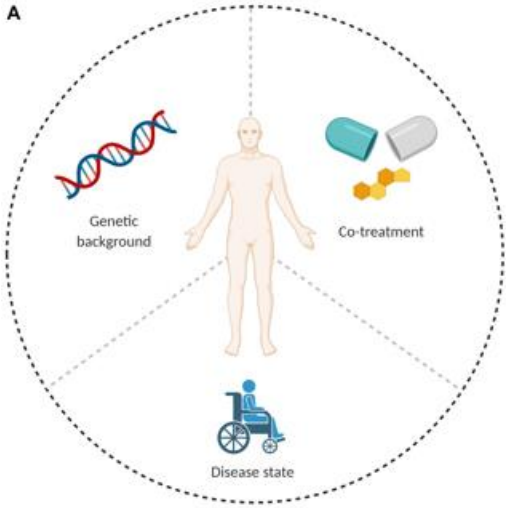


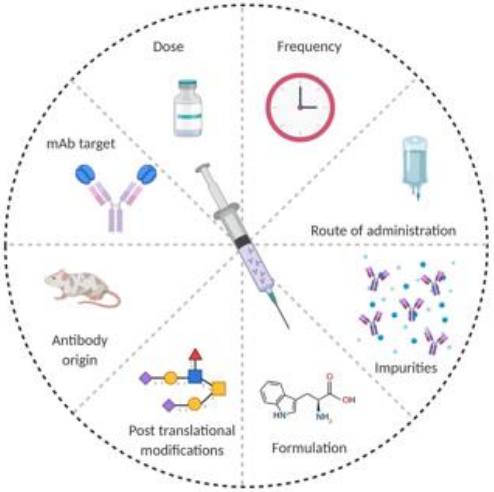
J Clin Med. 2023 May 4;12(9):3271.

Η δημιουργία ADAbs είναι αναπόφευκτη…



Η εμφάνιση αντιφαρμακευτικών αντισωμάτων εξαρτάται από πολλούς παράγοντες:





Σχετιζόμενοι με τον ασθενή

- Γενετική προδιάθεση (HLADQ5A1*05)
- BMI>25
- Κάπνισμα
- Νόσος (PA>ΨA>ΣπA)
- Ενεργότητα νόσου

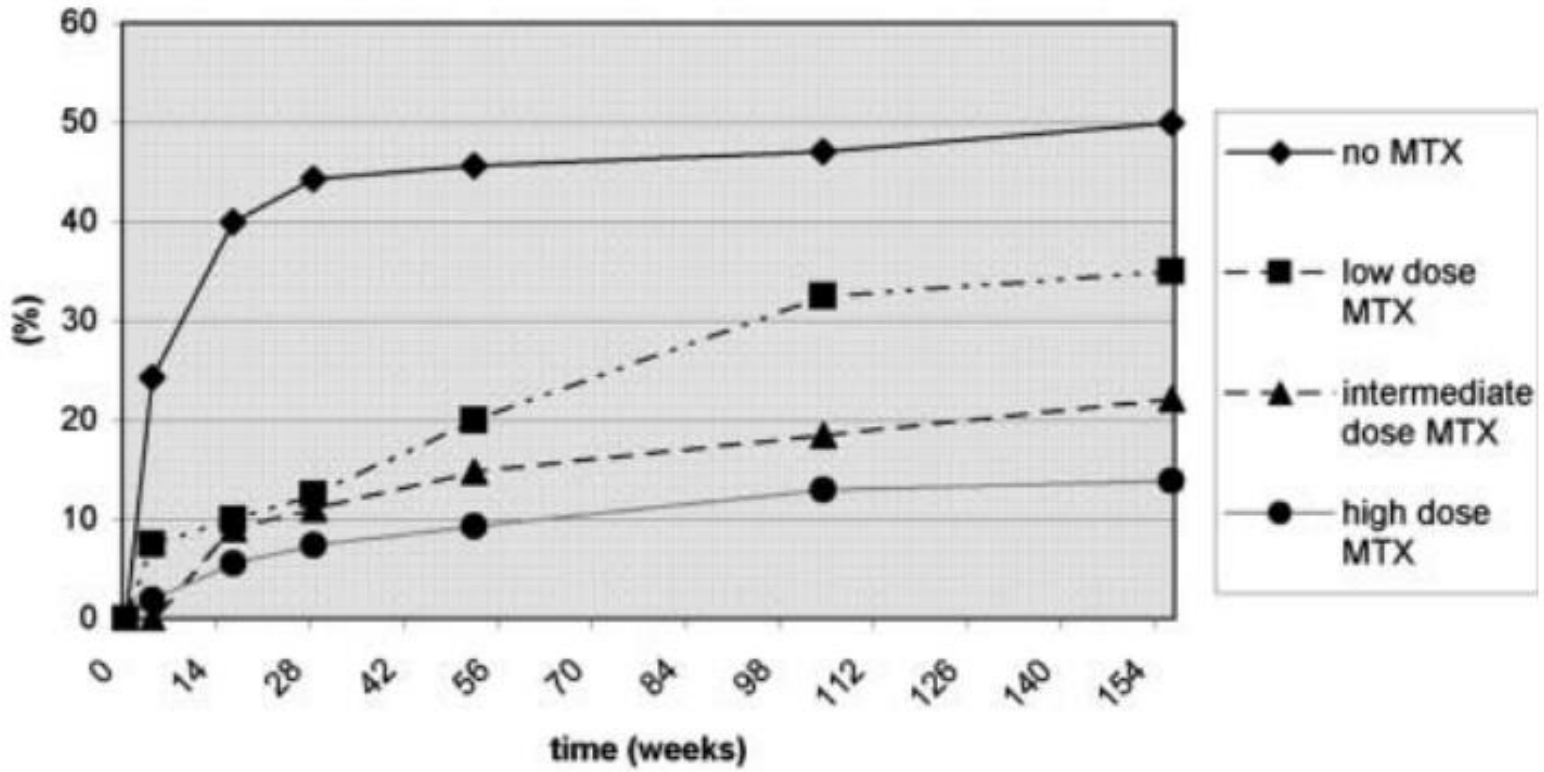
Σχετιζόμενοι με το φάρμακο

- Δόση
- Συχνότητα (drug holiday > συνεχής)
- Οδός χορήγησης (sc>iv)
- Συγχορηγούμενα φάρμακα (MTX)

Front Immunol. 2020 Aug 18:11:1951.

Η MTX ελαττώνει την παραγωγή ADAbs
- για το adalimumab η επίδραση αυτή φαίνεται να είναι δοσοεξαρτώμενη

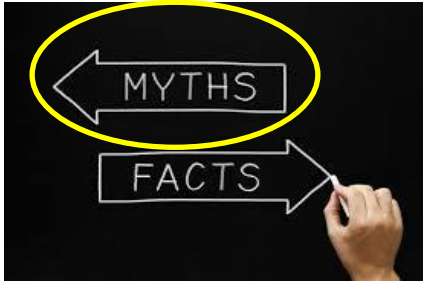
50% των ασθενών σε μονοθεραπεία με ADA αναπτύσσει ADAbs



Percentage of patients developing antiadalimumab antibodies per baseline MTX dose group. No MTX (0 mg/week, n=70), low dose MTX (5–10 mg/week, n=40), intermediate dose MTX (12.5–20 mg/week, n=54), or high dose MTX (≥22.5 mg/week, n=108).

Krieckaert CL, et al. *Ann Rheum Dis* 2012;71:1914–1915

Αφορούν μόνο τους aTNF…?



The humanization of mAbs has reduced the immunogenicity of biological agents

Biological Agent	Abbreviation	ADAs% Min–Max	Nabs% Min–Max
Infliximab	IFX	0–83.0	Not reported
Adalimumab	ADL	0–54.0	Not reported
Golimumab	GLM	0–19.0	Not reported
Etanercept	ETA	0–18.3	Not reported
Certolizumab pegol	CZP	3–37.0	Not reported
Rituximab	RTX	23.1–50.0	Not reported
Belimumab	BLM	0–4.8	Not reported
Abatacept	ABT	0.9–4.1	0–0.4
Tocilizumab	TCZ	0.7–2.0	0.8–1.3
Sarilumab	SLM	1.4–12.3	0–10.8
Secukinumab	SCK	0–1.0	Not reported
Ixekizumab	IXK	1.7–9.0	Not reported
Brodalumab	BDL	1.4–2.7	0
Ustekinumab	UTK	1.0–11.0	Not reported
Guselkumab	GKM	4.1–14.7	0.1–0.6
Risankizumab	RZM	14.1–31.0	2.1–16.0
Tildrakizumab	TZM	6.51–18.0	2.5–3.2
Anakinra	ANA	<1	Not reported
Canakinumab	CKM	3.1	0

J Clin Med. 2023 May 4;12(9):3271.

Μέθοδοι ανίχνευσης - μέτρησης

Types of assay.

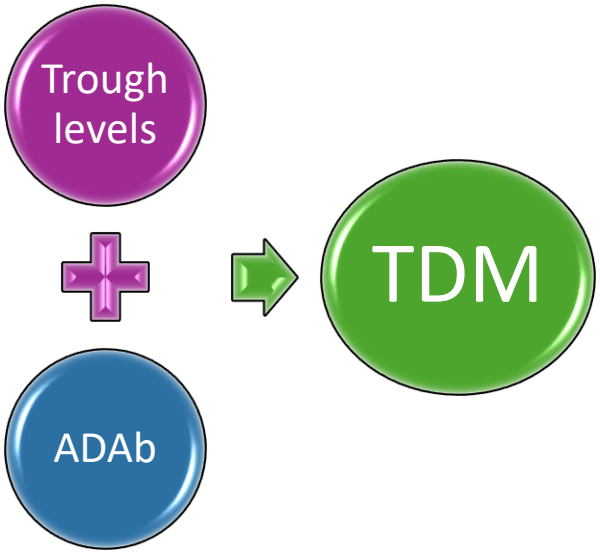
Type of assay	Basis	Advantages	Disadvantages	Main use
Capture ELISA	Solid phase analysis: plate covered with captured drug or with Fab fragments of a monoclonal antidrug	Convenient Fast Inexpensive Good sensitivity and specificity	Possible interference of RF (not when Fab fragments are used)	Throughput level testing
"Bridge" ELISA	Analysis in solid phase: plate covered with drug	Convenient Fast High sensitivity and specificity	★ False negatives for ADAs due to interference of the drug ★ False positives for ADAs due to RF ★ Does not detect IgG4 ADAs	ADA level testing
RIA	Analysis in liquid phase with drug or ^{131}I-labelled TNFα	More sensitive than ELISA for throughput level and ADA detection Less interference of the drug in ADA detection	Need for radioactive installation	Throughput level testing ADA testing
High mobility shift assay (HMSA)	High-resolution chromatography in liquid phase	Very sensitive No interference of the drug in the detection of ADAs	Very expensive Slow	Throughput level testing ADA testing
Functional	Bioluminescent analysis with cells that respond to TNF-α transfected with the luciferase gene	Detects drug biologically active in vivo and functionally relevant ADAs	Need to manage clones of living cells stored at -70 °C	Active drug testing Relevant ADA testing
Electrochemiluminescence	Uses an electrode covered with TNF to capture TNF α and an anti-PEG antibody as a detection reagent	More sensitive and specific than ELISA to measure drug and ADA levels. Less interference with the drug	Not very accessible, currently used in clinical trials, above all	Throughput and ADA level testing

ADA: anti-drug antibody; ELISA: enzyme immunoassay; Fab: fragment of the monoclonal antibody molecule that binds to the antigen; RF: rheumatoid factor; RIA: radioimmunoassay; TNF-α: tumour necrosis factor α.

EULAR points to consider for therapeutic drug monitoring of biopharmaceuticals in inflammatory rheumatic and musculoskeletal diseases

Therapeutic Drug Monitoring

Αναφέρεται στην αρχή της χρήσης φαρμακοκινητικών δεδομένων - συγκεντρώσεων του φαρμάκου στο αίμα και, προαιρετικά, ADAb, για τη βελτιστοποίηση της θεραπείας για έναν μεμονωμένο ασθενή



Krieckaert CLM, *et al*. *Ann Rheum Dis* 2023;**82**:65–73.

EULAR points to consider for therapeutic drug monitoring of biopharmaceuticals in inflammatory rheumatic and musculoskeletal diseases

Table 1 EULAR-endorsed overarching principles and points-to-consider for therapeutic drug monitoring (TDM) of biopharmaceuticals in inflammatory rheumatic and musculoskeletal diseases

		Grade of recommendation	Level of evidence	Level of agreement (0–10, mean (SD))	% of votes≥8/10
Points-to-consider					
1	Measurement of biopharmaceutical blood concentrations should be performed in a validated laboratory	C	2b	9.9 (0.3)	100
2	Measurement of ADAb should be performed in a validated laboratory, preferably using a consistent assay over time. Measurement should be performed and interpreted alongside contemporaneous biopharmaceutical blood concentrations	B - C	2b	9.8 (0.5)	100

EULAR advises to first measure the biopharmaceutical blood concentration and, **only in the case of absent or very low drug concentrations, ADAb testing could be performed.**

Krieckaert CLM, *et al*. *Ann Rheum Dis* 2023;**82**:65–73.

EULAR points to consider for therapeutic drug monitoring of biopharmaceuticals in inflammatory rheumatic and musculoskeletal diseases

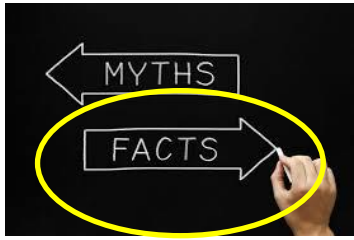
Reactive TDM could be considered in the management of inflammatory RMDs

Clinical scenarios

- Identify a reason for lack or loss or response
- Identify those with high biopharmaceutical blood concentrations in whom tapering may be indicated

Krieckaert CLM, *et al*. *Ann Rheum Dis* 2023;**82**:65–73.

Η παρουσία αντιφαρμακευτικών αντισωμάτων συσχετίζεται με απώλεια ανταπόκρισης στη θεραπεία

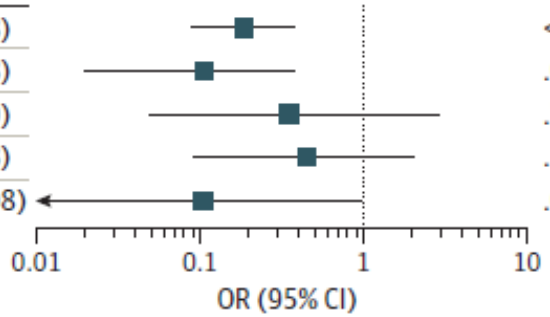


Outcome	Patients, No. (%)				
	With Anti-TNF mAb (n = 68)	Treated with etanercept (n = 82)	Treated with rituximab (n = 30)	Treated with tocilizumab (n = 50)	Overall (n = 230)
Overall antidrug antibody status					
Negative	24 (35.3)	47 (57.3)	14 (46.7)	23 (46.0)	108 (47.0)
Positive	26 (38.2)	5 (6.1)	15 (50.0)	10 (20.0)	56 (24.3)

Figure 2. Association of Response to Treatment With Antidrug Antibody Positivity

A Univariate logistic regression models of response to treatment explained by antidrug antibody positivity at month 12

bDMARD	Responders/analyzed patients, No./total No. (%)		OR (95% CI)	*P* value
	Responders (positive status)	Responders (negative status)		
All bDMARDs	27/56 (48)	90/108 (83)	0.19 (0.09-0.38)	<.001
anti-TNF mAbs	9/26 (35)	20/24 (83)	0.11 (0.02-0.38)	.001
Etanercept	3/5 (60)	38/47 (81)	0.35 (0.05-2.99)	.29
Rituximab	8/15 (53)	10/14 (71)	0.46 (0.09-2.08)	.32
Tocilizumab	7/10 (70)	22/23 (96)	0.11 (0.005-0.98)	.07



JAMA Network Open. 2023;6(7):e2323098.

Η παρουσία αντιφαρμακευτικών αντισωμάτων οδηγεί πάντα σε αποτυχία στη θεραπεία…?

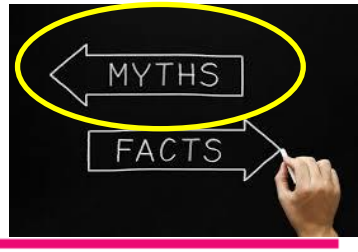
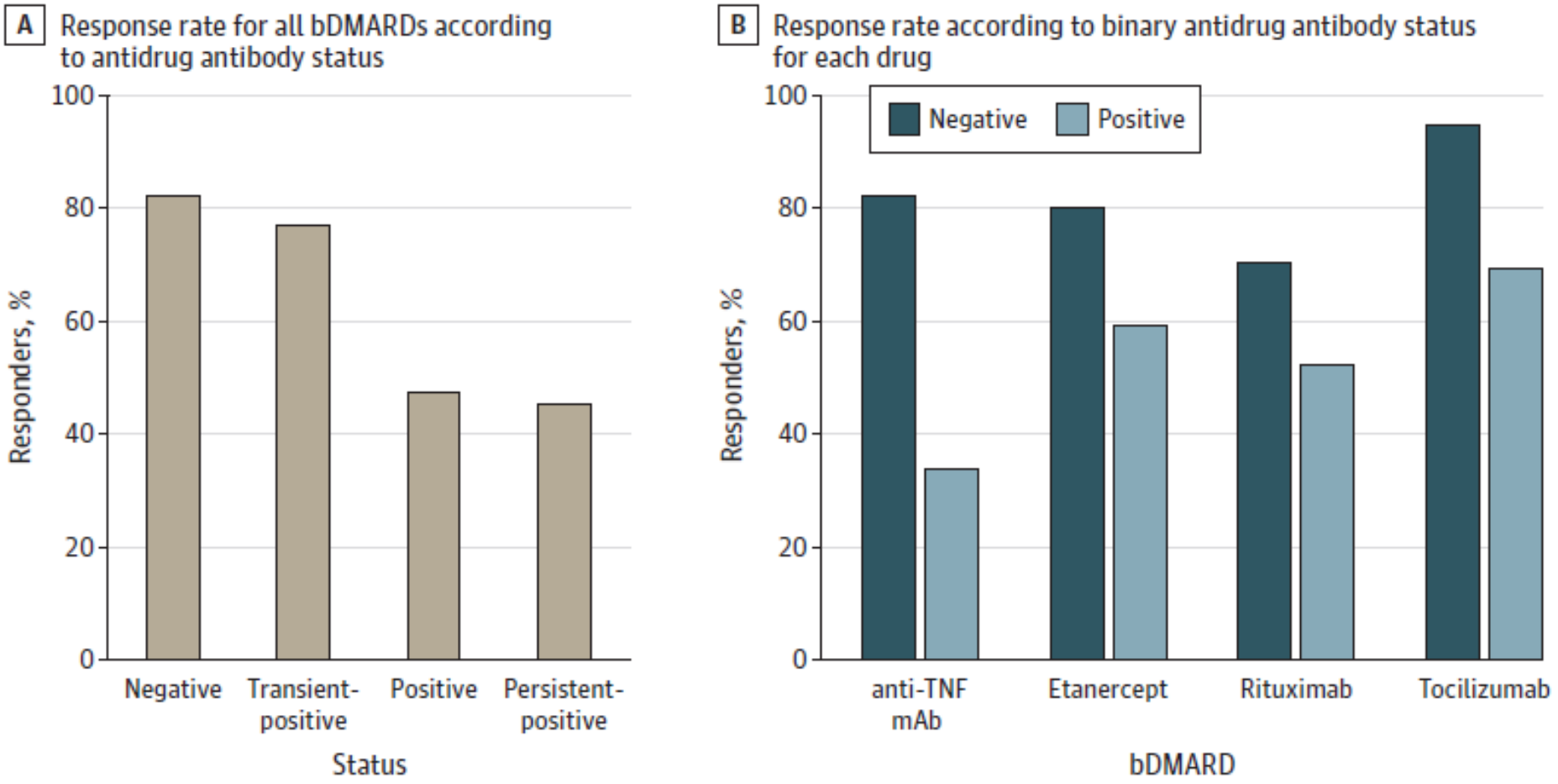
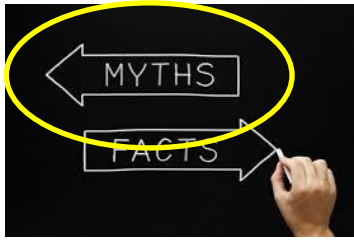


Figure 1. Response to Treatment and Antidrug Antibody Status at Month 12



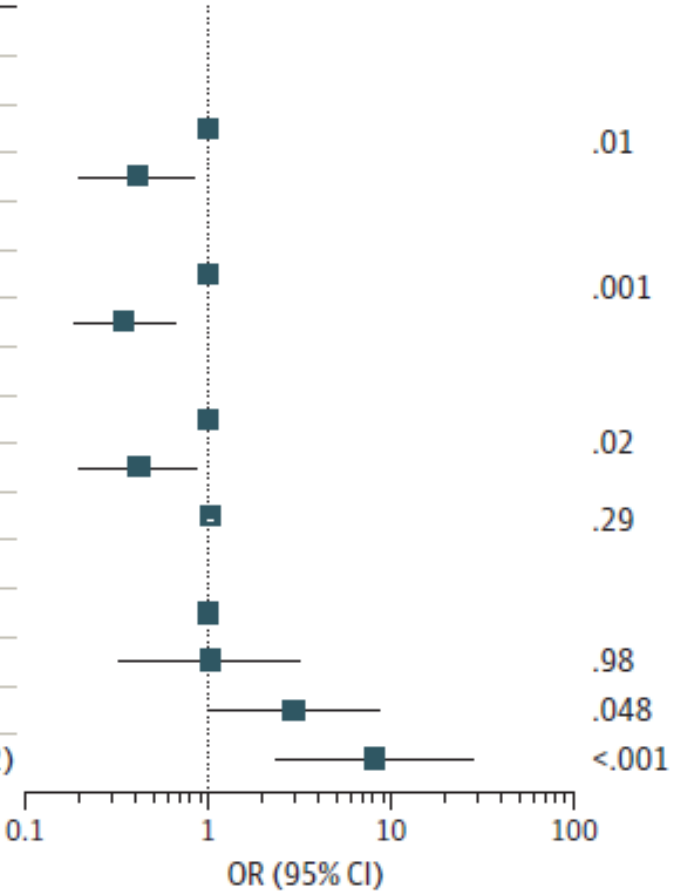
JAMA Network Open. 2023;6(7):e2323098.

Η απώλεια ανταπόκρισης στη θεραπεία εξαρτάται μόνο από τα αντιφαρμακευτικά αντισώματα…?

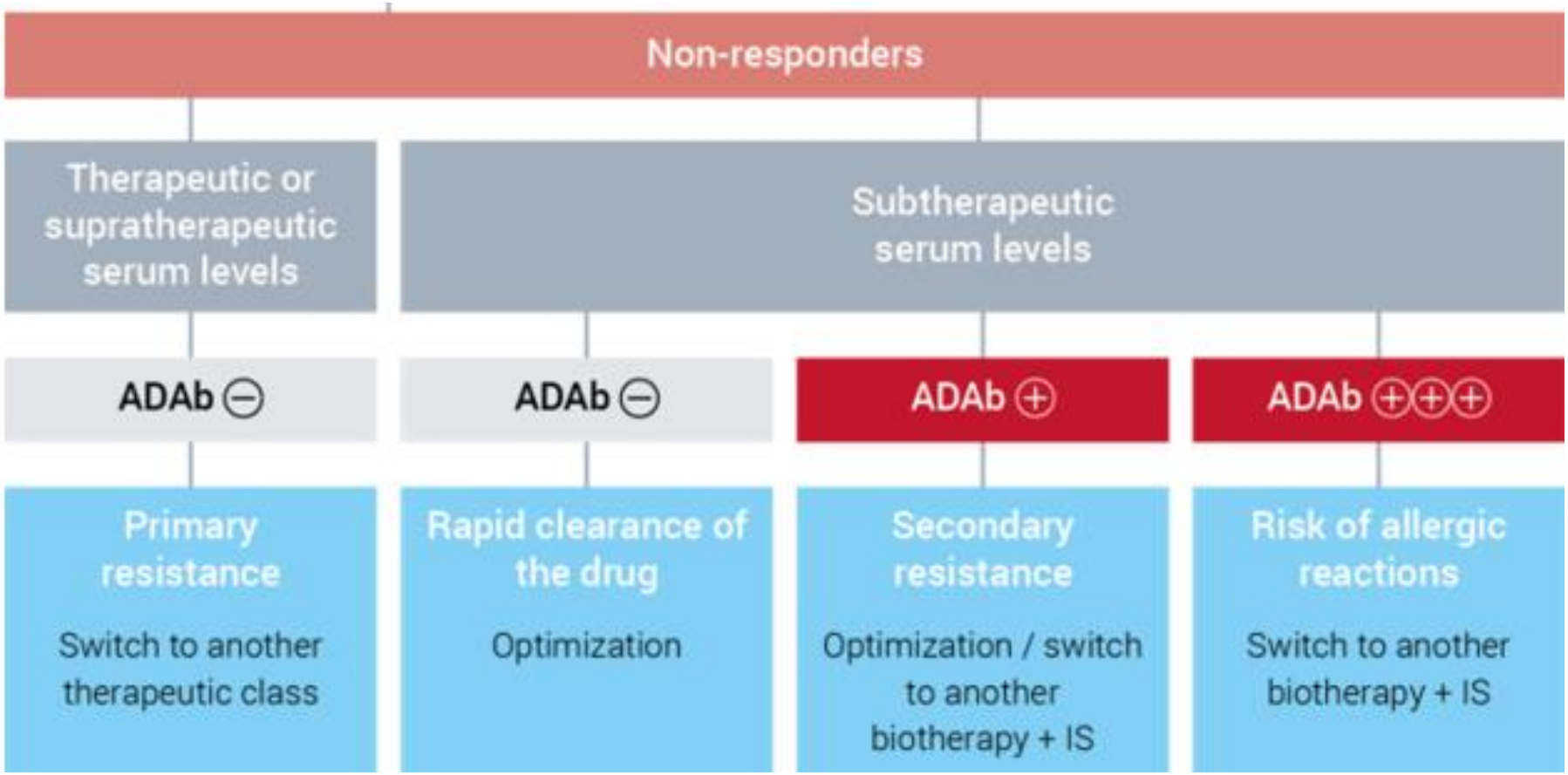


C Multivariable GEE model analysis accounting visits at months 6, 12, and 15-18

Variable	OR (95% CI)	*P* value
Patients, No.	166	
Antidrug antibody status		
Negative	1.00 [Reference]	.01
Positive	0.41 (0.20-0.83)	
BMI at visits		
<25	1.00 [Reference]	.001
≥25	0.35 (0.18-0.66)	
RF status at baseline		
Negative	1.00 [Reference]	.02
Positive	0.42 (0.20-0.87)	
Age at inclusion	1.01 (0.99-1.04)	.29
DAS28-CRP at baseline		
<2.6	1.00 [Reference]	
2.6-3.2	1.02 (0.32-3.20)	.98
>3.2-5.1	2.97 (1.01-8.72)	.048
>5.1	8.21 (2.37-28.42)	<.001



JAMA Network Open. 2023;6(7):e2323098.


Non-responders
Therapeutic or supratherapeutic serum levels
Subtherapeutic serum levels
ADAb ⊖
ADAb ⊖
ADAb ⊕
ADAb ⊕⊕⊕
Primary resistance
Switch to another therapeutic class
Rapid clearance of the drug
Optimization
Secondary resistance
Optimization / switch to another biotherapy + IS
Risk of allergic reactions
Switch to another biotherapy + IS

EULAR points to consider for therapeutic drug monitoring of biopharmaceuticals in inflammatory rheumatic and musculoskeletal diseases

Table 1 EULAR-endorsed overarching principles and points-to-consider for therapeutic drug monitoring (TDM) of biopharmaceuticals in inflammatory rheumatic and musculoskeletal diseases

	Grade of recommendation	Level of evidence	Level of agreement (0–10, mean (SD))	% of votes≥8/10
Despite an association with clinical response, the use of biopharmaceutical blood concentrations to guide dosing is not recommended due to the lack of an identified optimal range for most biopharmaceuticals in most indications.	B	2b	8 (2.2)	72

<u>Δε συστήνεται</u> μέτρηση των επιπέδων φαρμάκου για τον καθορισμό της δόσης

- Έλλειψη δεδομένων για τα θεραπευτικά επίπεδα για τα περισσότερα φάρμακα & για τις περισσότερες ενδείξεις

Krieckaert CLM, *et al*. *Ann Rheum Dis* 2023;**82**:65–73.

Επίπεδα φαρμάκων

Adalimumab (RA and PsA):

- blood concentrations of at least 1 mg/L, some clinical efficacy is evident in most patients.
- levels ≥6.0 mg/l associated with treatment response [odds ratio (OR) 2.2 (95% CI 1.0, 4.4)] and improved drug survival [hazard ratio 0.49 (95% CI 0.27, 0.80)].
- increasing blood concentrations efficacy improves further until approximately 8 mg/L, beyond which no additional benefit is seen at a population level.

Rheumatology (Oxford). 2024 May 3;63(6):1746-1755.

Infliximab

- Low infliximab trough concentrations (<3 mg/L) increase the risk of developing antidrug antibodies and secondary treatment failure in RA and IBD

Exploring TNFi drug-levels and anti-drug antibodies during tapering among patients with inflammatory arthritis: secondary analyses from the randomised BIODOPT trial

Dose reduction strategy

- 129 patients with RA, PsA, or axSpA on stable TNFi dose and in low disease activity≥12 months were randomised (2:1) to disease activity-guided tapering (n=88) or control (n=41)
- Disease activity was equivalent between groups at 18 months
- ADAb were detected in eight patients, all from the tapering group
- TNFi drug-level category or ADAb were not predictive for achieving successful tapering at 18 months.
- Data do not support using TNFi drug-level and/or ADAb to guide the tapering decision

Rheumatol Int. 2024 Oct;44(10):1897-1908.

Recommendation

EULAR points to consider for therapeutic drug monitoring of biopharmaceuticals in inflammatory rheumatic and musculoskeletal diseases

Routine use of proactive TDM is not recommended in the management of inflammatory RMDs

NOR-DRUM A trial

- Individualized drug dosing based on scheduled monitoring of serum drug levels (IFX) and ADAb
- Randomized, open-label clinical trial of 411 adults with RA, SpA, PsA, UC, Crohn or Ps
- Primary end point was clinical remission at week 30
- Clinical remission at week 30 was achieved in 100 (50.5%) of 198 and 106 (53.0%) of 200 patients in the TDM and standard therapy groups, respectively
- Adverse events were reported in 135 patients (68%) and 139 patients (70%) in the TDM and standard therapy groups, respectively.

JAMA. 2021 May 4;325(17):1744-1754.

Krieckaert CLM, *et al*. *Ann Rheum Dis* 2023;**82**:65–73.

Effect of Therapeutic Drug Monitoring vs Standard Therapy During Maintenance Infliximab Therapy on Disease Control in Patients With Immune-Mediated Inflammatory Diseases: A Randomized Clinical Trial

NOR-DRUM B

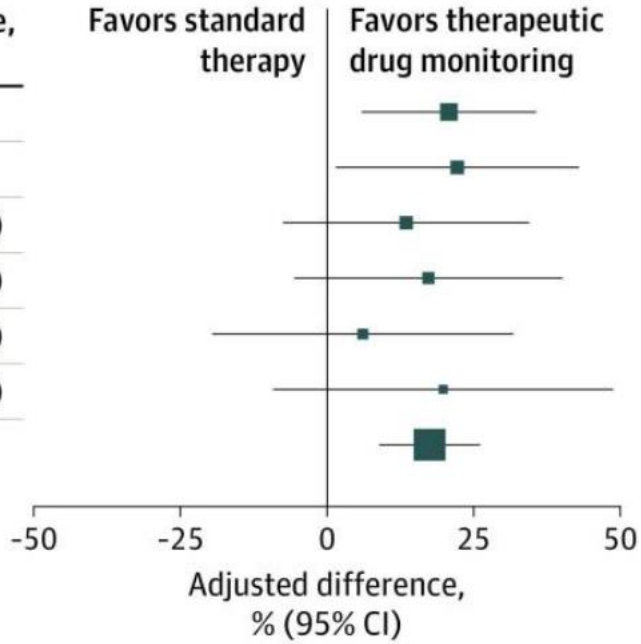
- Individualized drug dosing based on scheduled monitoring of serum drug levels (IFX) and ADAb
- 458 adults with RA, SpA, PsA, UC, Crohn or Ps
- Primary outcome: sustained disease control without disease worsening, 52w
- The primary outcome was observed in:
  - 167 patients (73.6%) in the TDM group
  - 127 patients (55.9%) in the standard therapy group
  - The estimated adjusted difference was 17.6% (95% CI, 9.0%-26.2%; P < .001) favoring TDM

JAMA. 2021 Dec 21;326(23):2375-2384.

Effect of Therapeutic Drug Monitoring vs Standard Therapy During Maintenance Infliximab Therapy on Disease Control in Patients With Immune-Mediated Inflammatory Diseases: A Randomized Clinical Trial

NOR-DRUM B

	Sustained disease control, No./total (%)		
	Therapeutic drug monitoring	Standard therapy	Adjusted difference, % (95% CI)
Spondyloarthritis	54/68 (79.4)	41/70 (58.6)	20.9 (6.0 to 35.8)
Ulcerative colitis	27/38 (71.1)	21/43 (48.8)	22.3 (1.6 to 43.1)
Rheumatoid arthritis	27/39 (69.2)	22/40 (55.0)	13.6 (-7.4 to 34.6)
Crohn disease	24/34 (70.6)	17/32 (53.1)	17.4 (-5.5 to 40.3)
Psoriatic arthritis	19/28 (67.9)	16/25 (64.0)	6.2 (-19.5 to 31.9)
Psoriasis	16/20 (80.0)	10/17 (58.8)	19.9 (-9.1 to 48.9)
Overall	167/227 (73.6)	127/227 (55.9)	17.6 (9.0 to 26.2)



JAMA. 2021 Dec 21;326(23):2375-2384.

Clinical consequences of infliximab immunogenicity and the effect of proactive therapeutic drug monitoring: exploratory analyses of the randomised, controlled NOR-DRUM trials

Marthe Kirkesæther Brun, Johanna E Gehin, Kristin Hammersbøen Bjørlykke, David John Warren, Rolf A Klaasen, Joseph Sexton, Øystein Sandanger, Tore K Kvien, Cato Mørk, Jørgen Jahnsen, Nils Bolstad, Kristin Kaasen Jørgensen, Espen A Haavardsholm*, Guro Løvik Goll*, Silje Watterdal Syversen**

- 616 patients (mean age: 45 years, 305 (50%) patients were women)
- Antidrug antibodies were detected in 147 (24%) patients.

- Patients with antidrug antibodies vs patients w/o antidrug antibodies, higher rates were found for:
  - disease worsening over 52 weeks (0·76 per person-year *vs* 0· 35 per person-year, hazard ratio [HR] 2·02 [95% CI 1·33–3·07]; p=0·0009)
  - infusion reactions (0·16 per person-year *vs* 0·03 per person-year, HR 17·02 [6·98–41·47]; p<0·0001)
  - infliximab discontinuation (1·00 per person-year *vs* 0·20 per person-year, HR 6·64 [4·84–9·11]; p<0·0001)
- These associations were more pronounced in patients with high concentrations of antidrug antibodies than in those with low concentrations.

Lancet Rheumatol. 2024 Apr;6(4):e226-e236.

EULAR points to consider for therapeutic drug monitoring of biopharmaceuticals in inflammatory rheumatic and musculoskeletal diseases

- Measurement of ADAb should be considered in the case of a hypersensitivity reaction, mainly related to infusions
  - In the specific case of hypersensitivity reactions, the task force could justify measuring ADAb without biopharmaceutical blood concentrations.

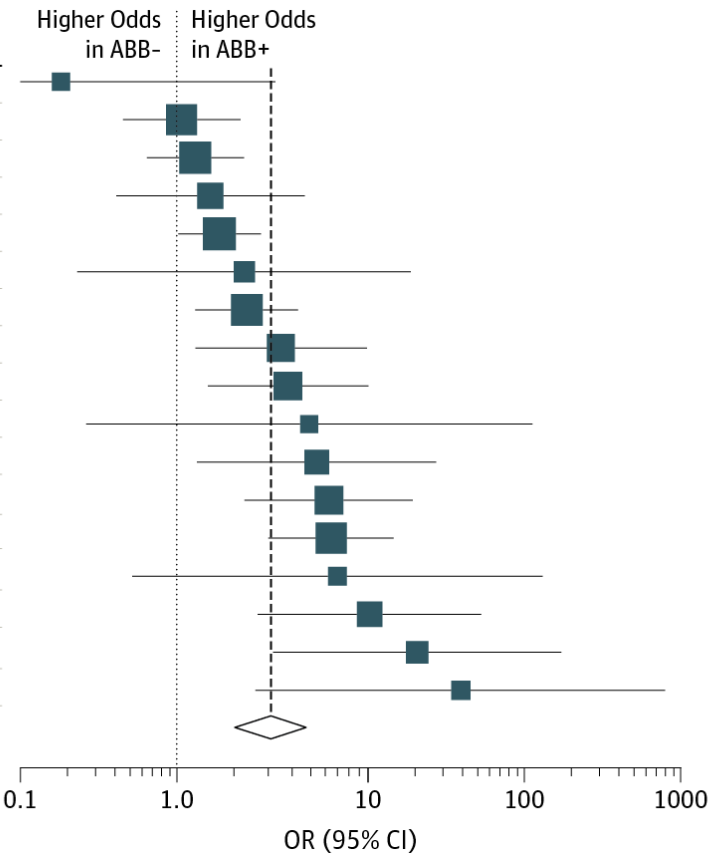
- Measurement of ADAb is not recommended in the case of an injection-site reaction

Krieckaert CLM, *et al*. *Ann Rheum Dis* 2023;**82**:65–73.

Η παρουσία ADAs έναντι του infliximab σχετίζεται με αντιδράσεις κατά την έγχυση

- Σχετικός κίνδυνος x2-x4

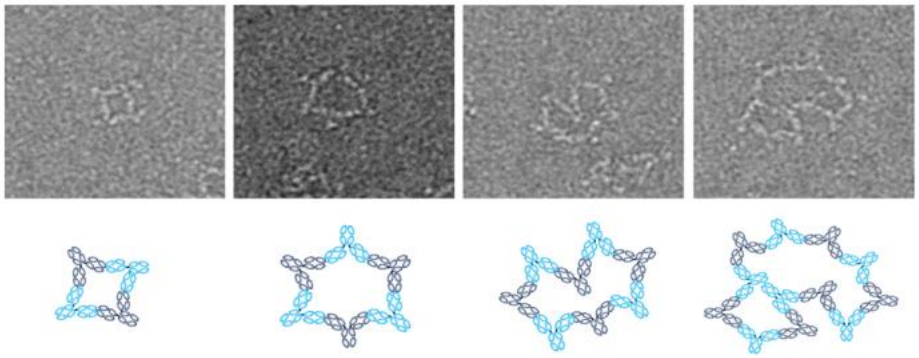
Source	No. of Patients	OR (95% CI)	Weight, %
Bender et al,[57] 2007	15	0.18 (0.01-4.26)	2.20
Gottlieb et al,[31] 2004	249	1.07 (0.45-2.55)	8.76
Abe et al,[56] 2006	129	1.31 (0.64-2.69)	9.49
Asahina et al,[25] 2010	169	1.64 (0.41-6.59)	6.34
Hanauer et al,[32] 2002	573	1.87 (1.01-3.46)	9.97
Hyams et al,[33] 2007	112	2.69 (0.23-31.43)	3.23
Sands et al,[53] 2004	195	2.79 (1.30-5.96)	9.28
Ruperto et al,[48] 2010	72	4.64 (1.31-16.42)	6.87
Rutgeerts et al,[49] 2005, ACT1	243	5.13 (1.57-16.74)	7.24
de Vries et al,[67] 2009	35	7.00 (0.26-186.26)	2.07
Farrell et al,[30] 2003, OBS	53	7.80 (1.34-45.28)	4.98
Rutgeerts et al,[49] 2005, ACT2	241	9.35 (2.71-32.23)	7.00
Braun et al,[26] 2008	279	9.64 (3.84-24.25)	8.49
Wolbink et al,[8] 2006	51	10.59 (0.52-216.54)	2.37
Plasencia et al,[68] 2011	94	17.00 (3.29-87.85)	5.38
Ben-Horin et al,[75] 2011	62	34.29 (4.12-285.48)	3.96
de Vries et al,[66] 2007	38	65.00 (3.18-1330.09)	2.37
Overall: I^2 = 62.5%, P <.001		3.97 (2.36-6.67)	100.00



JAMA Intern Med. 2013;173(15):1416-1428

Οι περισσότεροι ασθενείς υπό Infliximab & ADAs ΔΕΝ εμφανίζουν αντιδράσεις κατά την έγχυση του φαρμάκου

- Παράγοντες που φαίνεται να συμβάλλουν στην εμφάνιση ανεπιθύμητων ενεργειών είναι το μέγεθος και το σχήμα των συμπλεγμάτων TNFi-ADA.
- Η πλειονότητα των συμπλοκών είναι διμερή (ένα φαρμακευτικό αντίσωμα δεσμευμένο σε ένα TNFi).
- Κάτω από συγκεκριμένες συνθήκες μεγαλύτερα σύμπλοκα (τετραμερή, εξαμερή, κ.λπ.) μπορούν να σχηματιστούν.
- Τα μεγάλα, ακανόνιστου σχήματος συμπλέγματα είναι ικανά να ενεργοποιήσουν το συμπλήρωμα.



van Schie KA, *et al*. *Ann Rheum Dis* 2018;**0**:1–9.

Real-life drug retention rate and safety of rituximab when treating rheumatic diseases: a single-centre Swiss retrospective cohort study

Alexandre Dumusc[1,2*], Fahad Alromaih[1], Matthieu Perreau[3,2], Thomas Hügle[1,2], Pascal Zufferey[1,2] and Diana Dan[1,2]

- ADAs were observed in 18% of the patients

- Detection of ADAs was positively associated with:
  - anti-SSA positivity (OR 4.95 [95% CI 1.16, 21.1]),
  - concomitant use of hydroxychloroquine (OR 4.88 [95% CI 1.17, 20.4])
  - diagnosis of CTD (OR 6.5 [95% CI 1.19, 35.6])

  and negatively associated with:
  - RF positivity (OR 0.17 [95% CI 0.04, 0.79])
  - previous treatment with MTX (OR 0.16 [95% CI 0.04, 0.65]).

- ADAs were detected in 63% of infusions-related SAE

Arthritis Res Ther. 2023 Jun 1;25(1):91.

Efficacy, safety, and cost-effectiveness of therapeutic drug monitoring (TDM) for TNF inhibitor therapy in rheumatic disease: A systematic review and meta-analysis

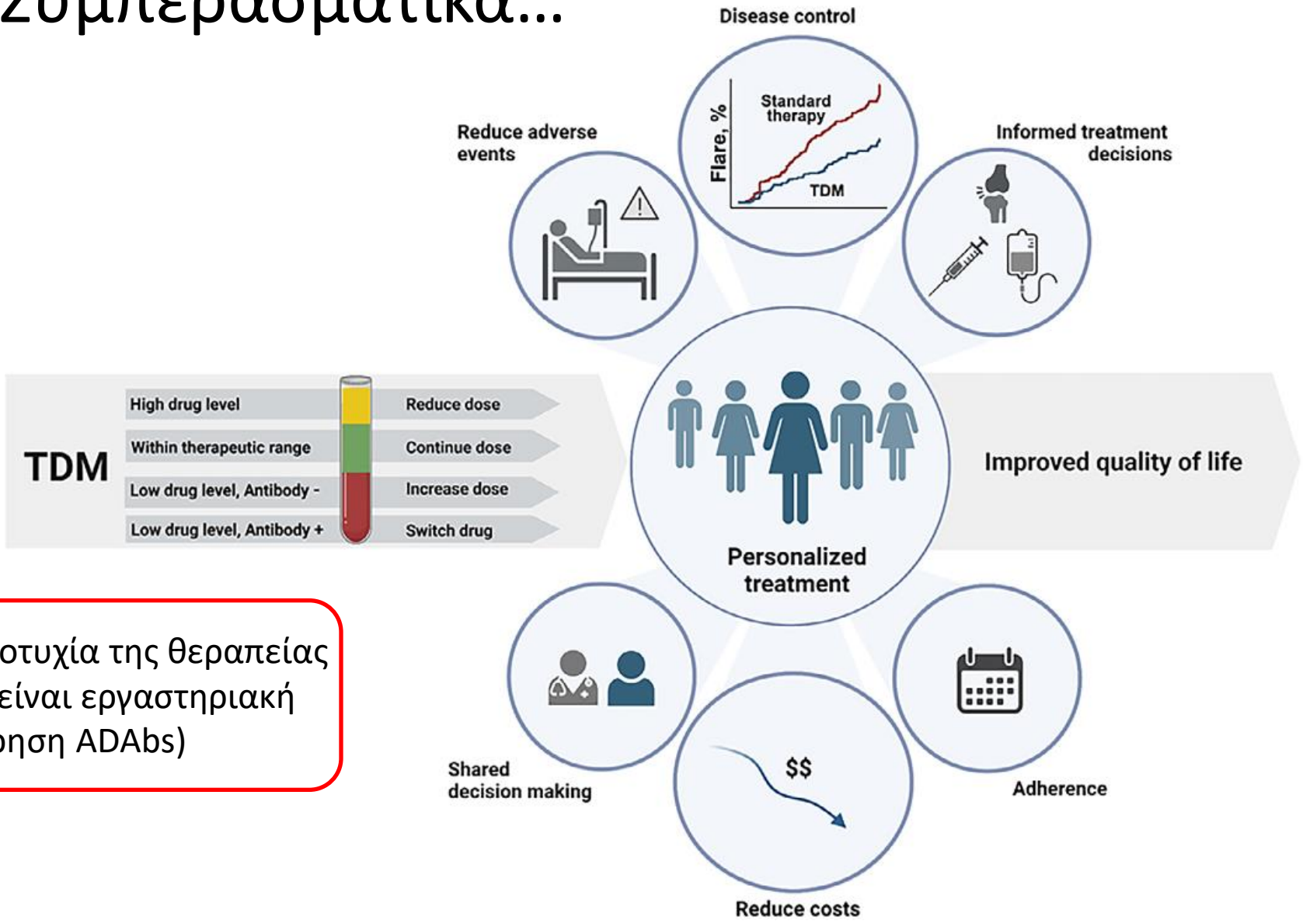
Cost-effectiveness?

14 studies (eight RCTs and six cohort studies) - 2427 patients

Patients receiving TDM-guided therapy had reduced cost per patient per year (calculated as the total accumulated sum of therapy cost).

- Spain - total cost saving was approximately €153,798/year (Pascual-Salcedo et al.).
- Spain –estimated saving per patient-year was 6-8 % (Ucar and Arango).
- the Netherlands – drug costs can be reduced by 33 % annually per patient based on the cost of standard-dosing adalimumab treatment (I'Ami et al)

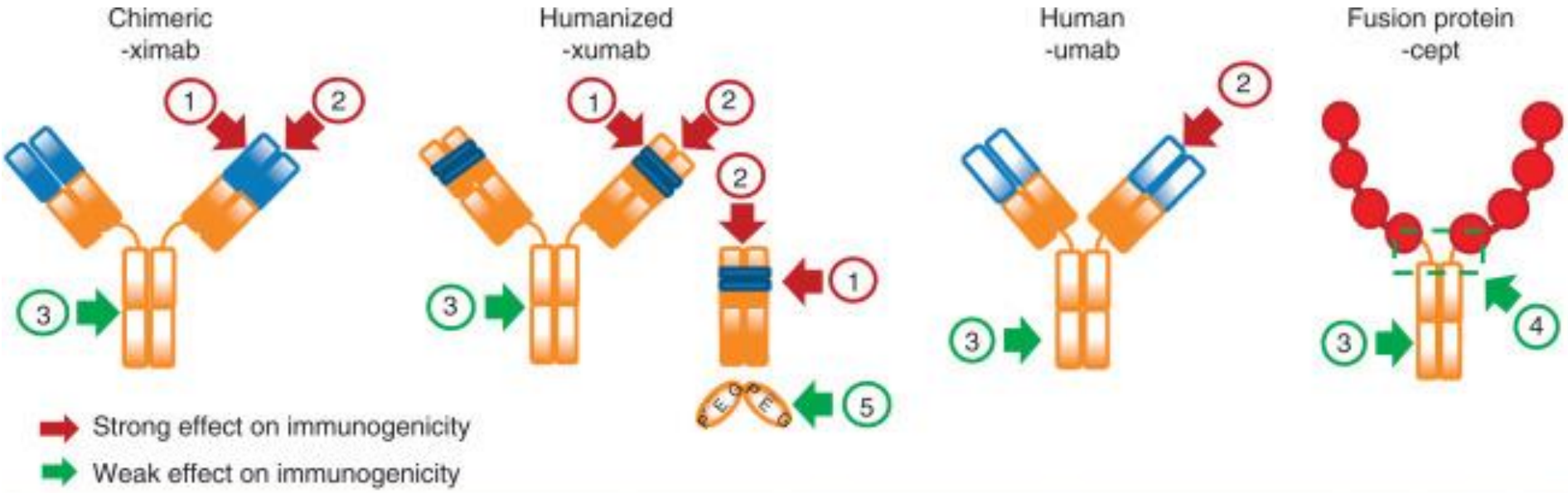
Συμπερασματικά…



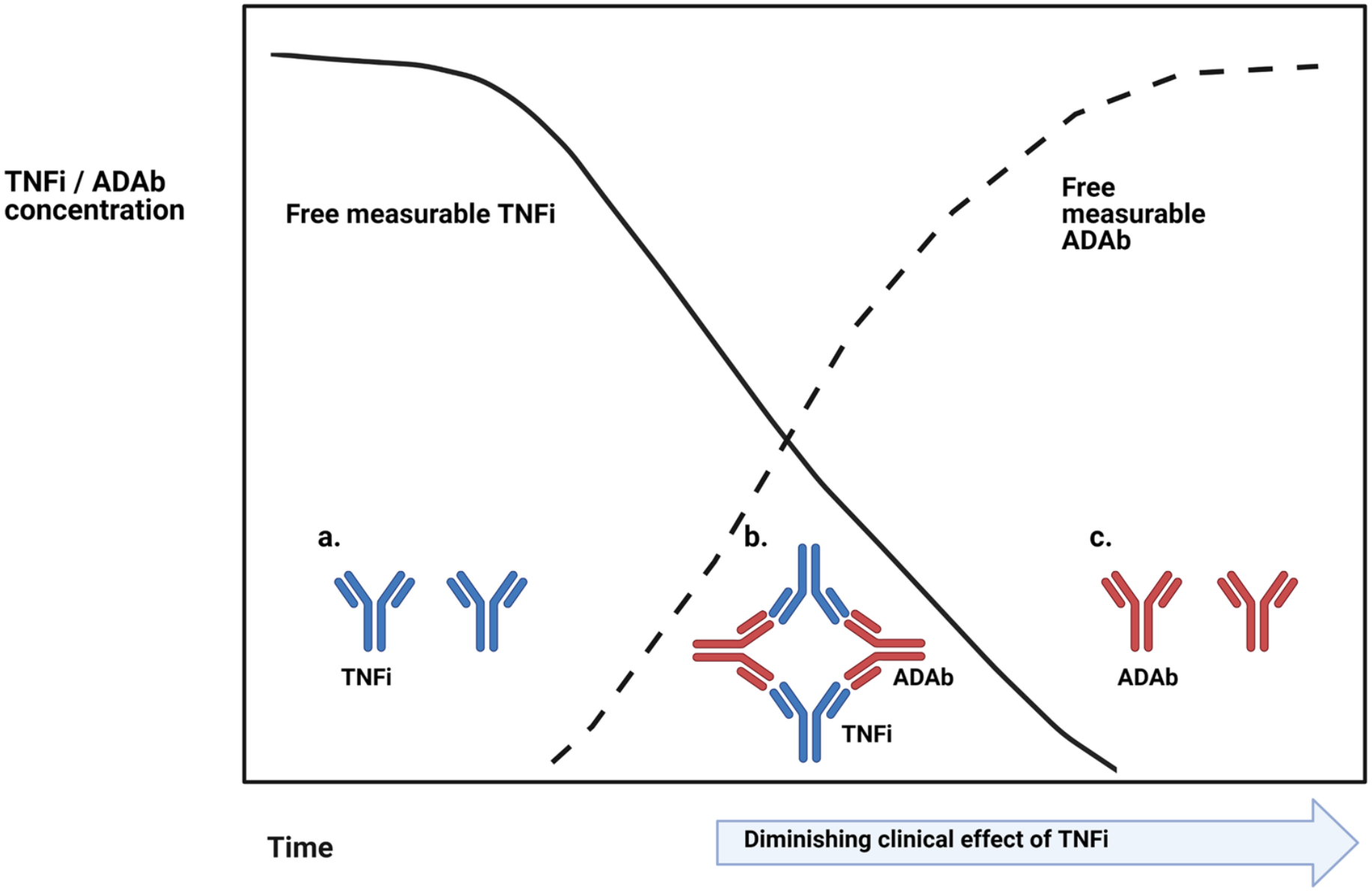
Η αποτυχία της θεραπείας ΔΕΝ είναι εργαστηριακή (μέτρηση ADAbs)

Ευχαριστώ

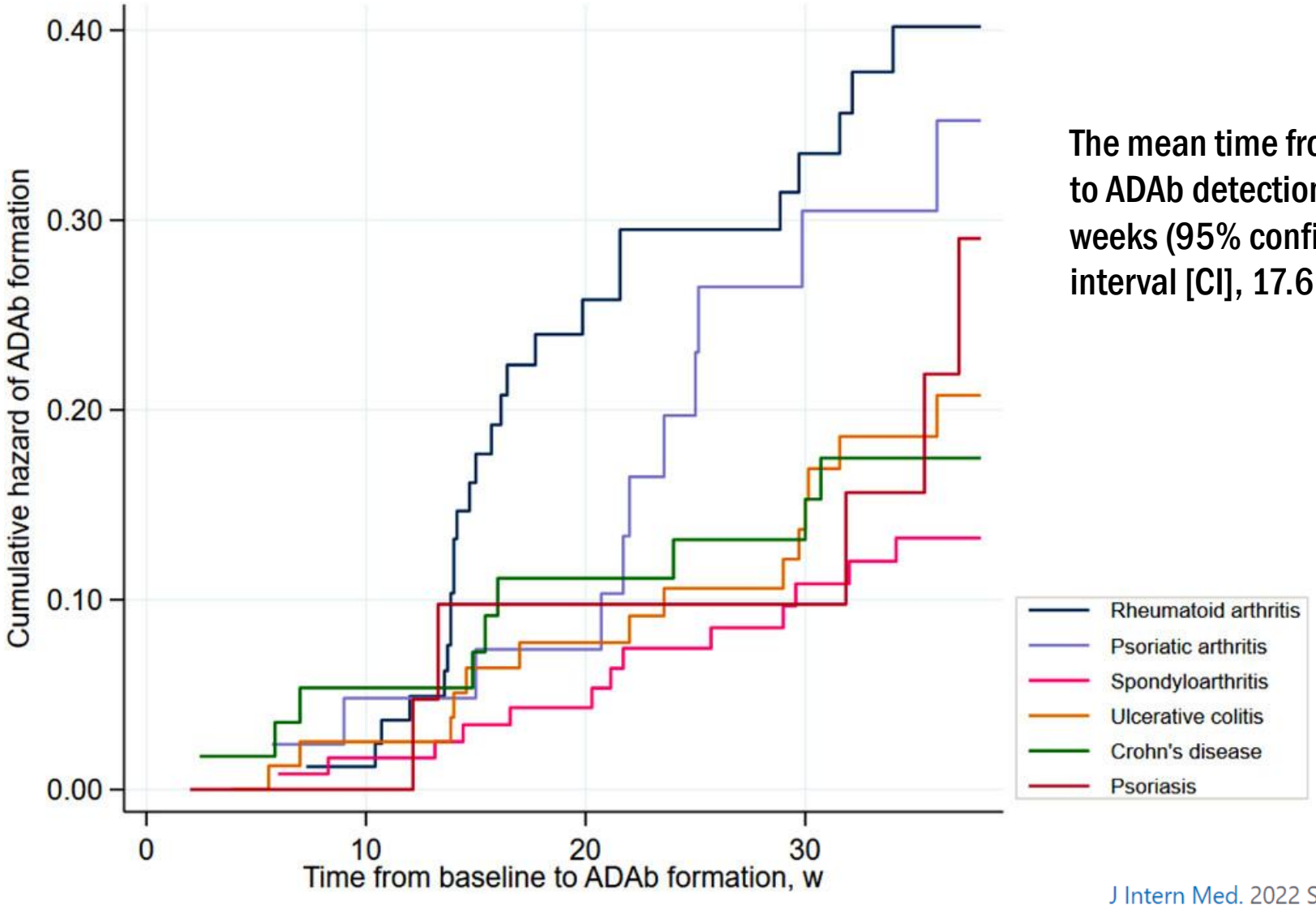
- Appendix



1. Murine epitope: Murine complementarity-derived regions±framework regions of Fab
2. Idiotope: Molecular structure in the variable region of Fab that confers antigenic specificity. Idiotopes may be allocated at the antigen-binding site or on variable region sequences outside of it
3. Allotope: Genetic variants within the constant region sequences of particular isotypes (k, IgG1-chains), i.e., patients not endowed with a given allotype may generate ADAs against this allotope if it is present on the drug
4. Human neo-antigens: Joining region of fusion proteins
5. Polyethylene glycol (PEG) moiety: Clinical relevance of anti-PEG antibodies is debated


TNFi / ADAb concentration
Free measurable TNFi
Free measurable ADAb
a.
TNFi
b.
ADAb
TNFi
c.
ADAb
Time
Diminishing clinical effect of TNFi

Πότε εμφανίζονται?



The mean time from baseline to ADAb detection was 19.7 weeks (95% confidence interval [CI], 17.6–21.8).

J Intern Med. 2022 Sep;292(3):477-491.

Biological	Prevalence of anti-drug antibodies % range (number of studies)		
	Rheumatoid Arthritis	Spondyloarthritis	Range
Abatacept[a]	2–20 (7)		2–20 (9)
Adalimumab[a,b]	0–51 (33)	8–39 (9)	0–54 (56)
Certolizumab-Pegol[a,b]	2.8–37 (7)		3–37 (7)
Etanercept[a,b]	0–13 (25)	0 (4)	0–13 (34)
Golimumab[a,b]	2–10 (11)	0–6.4 (2)	0–10 (14)
Infliximab[a,b]	8–62 (48)	6.1–69 (10)	6–62 (63)
Rituximab[a]	0–21 (8)		0–21 (8)
Secukinumab[c]		0–.3 (3)	0–0.5 (6)
Tocilizumab[a]	0–16 (14)		0–16 (17)
CT-P13[a,b,d]	26–52 (2)	27 (1)	21–52 (3)

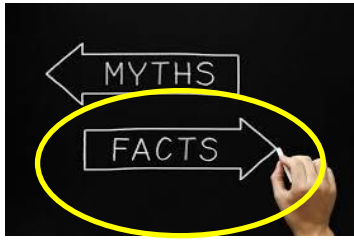
Therapeutic Drug Monitoring (TDM)

Αναφέρεται στην αρχή της χρήσης φαρμακοκινητικών δεδομένων - συγκεντρώσεων του φαρμάκου στο αίμα και, προαιρετικά, ADAb, για τη βελτιστοποίηση της θεραπείας για έναν μεμονωμένο ασθενή

Reactive TDM – in response to a clinical scenario (disease activity) to adjust subsequent therapy

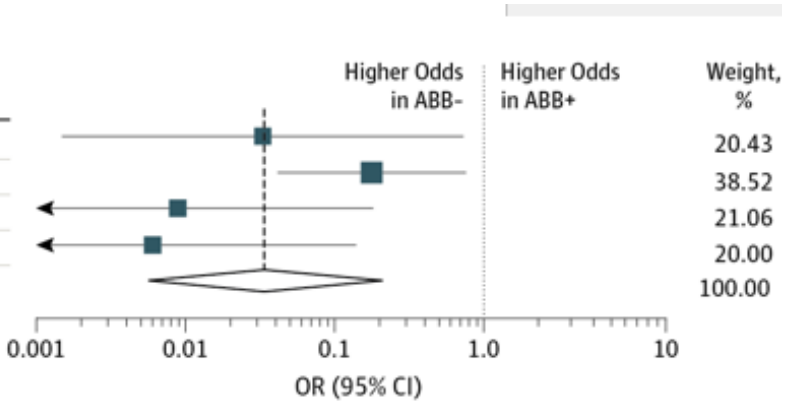
Proactive TDM – monitoring in a scheduled, preemptive fashion, with the concept of optimizing therapy to prevent future disease activity

Η παρουσία αντιφαρμακευτικών αντισωμάτων συσχετίζεται με απώλεια ανταπόκρισης στη θεραπεία



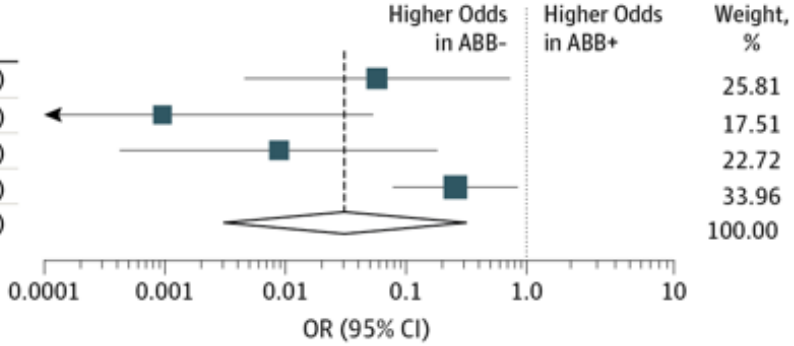
A

Source	No. of Patients	OR (95% CI)
Geborek et al,[60] 2005	20	0.03 (0.00-0.72)
Pascual-Salcedo et al,[62] 2011	51	0.18 (0.04-0.75)
Radstake et al,[63] 2009, IFX	35	0.01 (0.00-0.18)
Radstake et al,[63] 2009, ADA	34	0.01 (0.00-0.14)
Overall: I^2 = 49.6%, P = .11		0.03 (0.01-0.21)



B

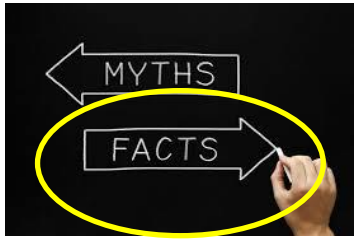
Source	No. of Patients	OR (95% CI)
Pascual-Salcedo et al,[62] 2011	31	0.06 (0.00-0.71)
Radstake et al,[63] 2009, IFX	34	0.00 (0.00-0.05)
Radstake et al,[63] 2009, ADA	35	0.01 (0.00-0.18)
Wolbink et al,[8] 2006	51	0.26 (0.08-0.83)
Overall: I^2 = 71.1%, P = .02		0.03 (0.00-0.30)



A, Association with EULAR response at 6 months or less.
B, Association with EULAR response at 6 months or more.

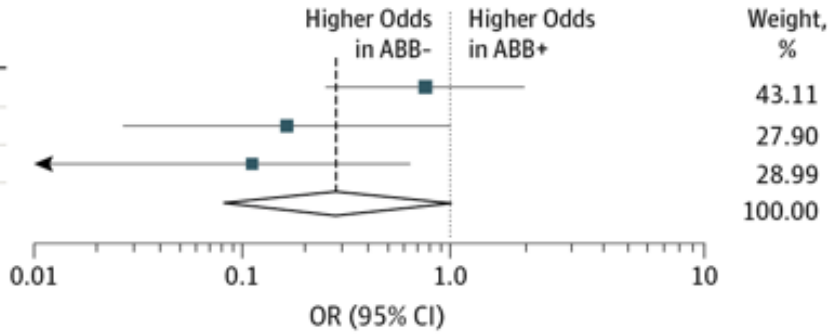
JAMA Intern Med. 2013;173(15):1416-1428

Η παρουσία αντιφαρμακευτικών αντισωμάτων συσχετίζεται με απώλεια ανταπόκρισης στη θεραπεία



C

Source	No. of Patients	OR (95% CI)
Davis et al,[65] 2006	204	0.76 (0.25-2.28)
de Vries et al,[66] 2007	38	0.16 (0.03-1.00)
de Vries et al,[67] 2009	35	0.11 (0.02-0.64)
Overall: I^2 = 52.9%, P = .12		0.28 (0.08-1.03)



C, Association with Assessment in AS International Working Group response

JAMA Intern Med. 2013;173(15):1416-1428

Efficacy, safety, and cost-effectiveness of therapeutic drug monitoring (TDM) for TNF inhibitor therapy in rheumatic disease: A systematic review and meta-analysis

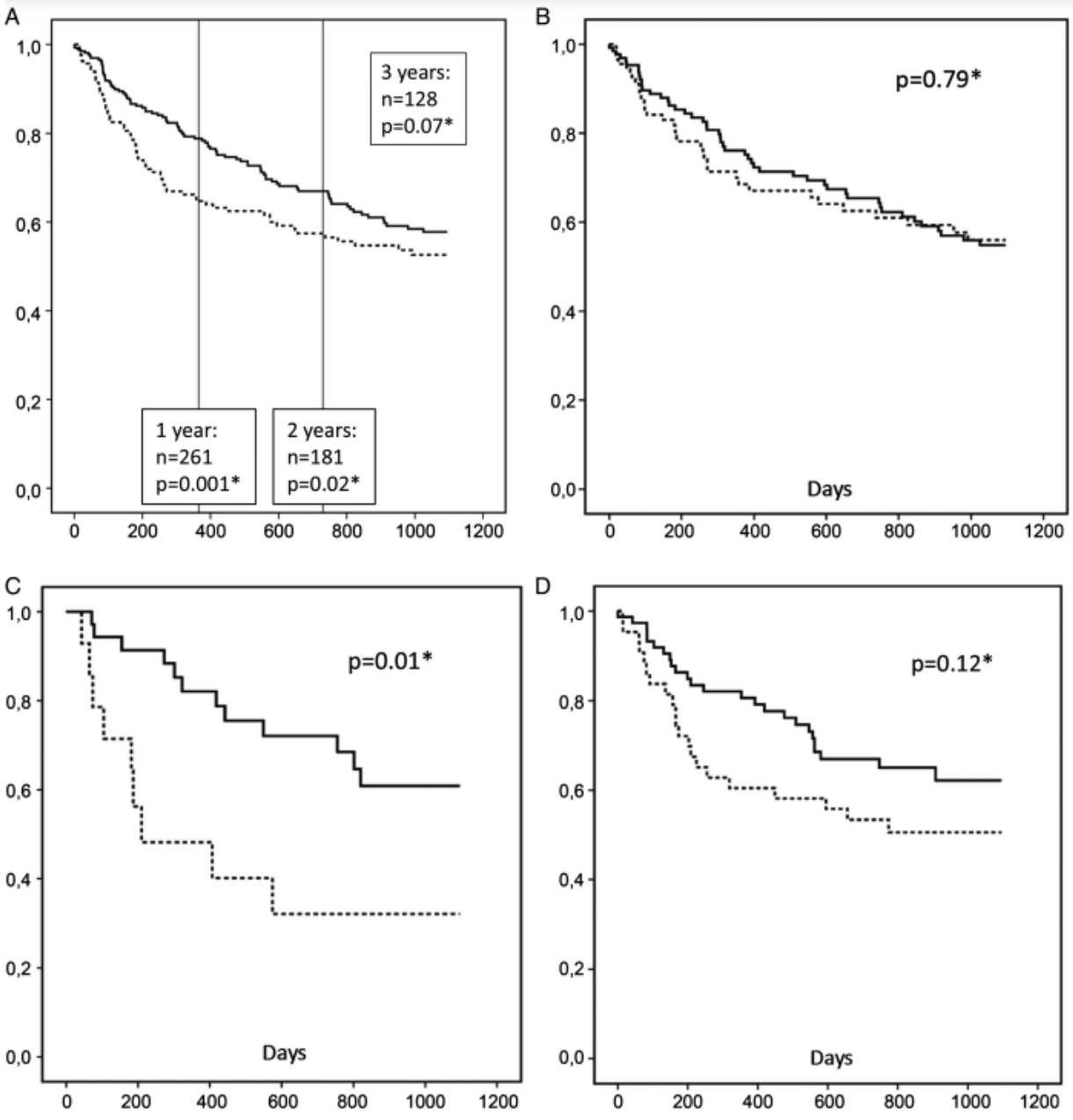
The overall results of meta-analysis for clinical efficacy outcomes.

Outcome	No. of studies	No. of patients	Events		Pooled RR (95 % CI)	*P* value[a]	I^2
			TDM-guided	Empirical-guided			
Prediction for response							
Treat-to-target	6	1375	384 (59.4 %)	390 (53.5 %)	1.3 (1.02, 1.65)	0.03	79 %
Clinical remission	2	852	227 (53.4 %)	233 (54.6 %)	0.98 (0.87, 1.11)	0.75	0 %
Low disease activity	3	217	68 (61.8 %)	29 (27.1 %)	2.11 (1.22, 3.66)	0.007	61 %
Prediction for successful dose reduction or discontinuation (TDM-guided therapy vs. standard dosing therapy)							
Relapse	4	452	104 (44.8 %)	82 (37.3 %)	1.24 (0.85, 1.80)	0.27	57 %
Radiographic progression-without structural damage progression	1	137	42 (65.6 %)	50 (68.5 %)	0.96 (0.76, 1.21)	0.72	\
Prediction for successful dose reduction or discontinuation (TDM-guided therapy vs. empirical-guided therapy)							
Relapse	2	319	135 (65.2 %)	100 (89.3 %)	0.73 (0.65, 0.82)	<0.00001	0 %

Efficacy, safety, and cost-effectiveness of therapeutic drug monitoring (TDM) for TNF inhibitor therapy in rheumatic disease: A systematic review and meta-analysis

Outcome	No. of studies	No. of patients	Mean±SD		Mean difference (95 % CI)	*P* value[a]	I^2
			TDM-guided	Empirical-guided			
Prediction for response							
Change of disease activity score (△DAS-28)	3	1091	\	\	-0.06 (-0.26. 0.15)	0.58	58 %
Change of disease activity score (△SDAI)	2	852	\	\	-0.06 (-2.03, 1.91)	0.95	60 %
Change of disease activity score (△BASDAI)	2	852	\	\	0.05 (-0.17, 0.27)	0.63	0
Prediction for successful dose reduction or discontinuation (TDM-guided therapy vs. standard dosing therapy)							
Mean disease activity score (DAS-28)	4	404	\	\	0.16 (-0.03, 0.35)	0.11	40 %
Mean disease activity score (BASDAI)	2	199	\	\	0.02 (-0.31, 0.35)	0.9	0
Radiographic progression-median vSHS	1	137	\	\	-6.20 (-21.14, 8.74)	0.42	\

The role of methotrexate co-medication in TNF-inhibitor treatment in patients with psoriatic arthritis: results from 440 patients included in the NOR-DMARD study



Drug survival by co-medication. (A) All patients. N, patients still observed at the end of the interval. (B–D) Drug survival by co-medication for patients starting etanercept, infliximab and adalimumab. *p Value by log-rank test.

Fagerli KM, *et al*. *Ann Rheum Dis* 2014;**73**:132–137.

RTX

- aim - whether development of ADAs against rituximab was associated with early B cell repopulation.
- 14/28 patients developed ADAs within 12 months of treatment.
- No association between ADA development and BCR depletion (early or late) was observed.
- Ten (71%) out of these 14 ADA positive patients showed B-cell repopulation within 12 months, while 4 out of 13 (30%) of the ADA negative patients did (*p*-value = 0.06, n.s)
- Hence, even though not significant, there still might be a trend in favor of an association between the development of anti-drugs antibodies within 12 months of treatment and repopulation of the B cell compartment within the same time-span.

Arthritis Res Ther. 2024 Mar 16;26(1):70.

EULAR points to consider for therapeutic drug monitoring of biopharmaceuticals in inflammatory rheumatic and musculoskeletal diseases

- Measurement of ADAb should be considered in the case of immunogenic biopharmaceuticals, alongside biopharmaceutical blood concentrations, at the time of clinical non-response

- Αντιφατικά στοιχεία σχετικά με το αν η παρουσία ADAb σε έναν πρώτο TNFi προβλέπει καλύτερη ανταπόκριση στη θεραπεία σε έναν δεύτερο TNFi ή μεγαλύτερη πιθανότητα ανάπτυξης αντισωμάτων στον δεύτερο TNFi

Krieckaert CLM, *et al*. *Ann Rheum Dis* 2023;**82**:65–73.

The presence or absence of antibodies to infliximab or adalimumab determines the outcome of switching to etanercept

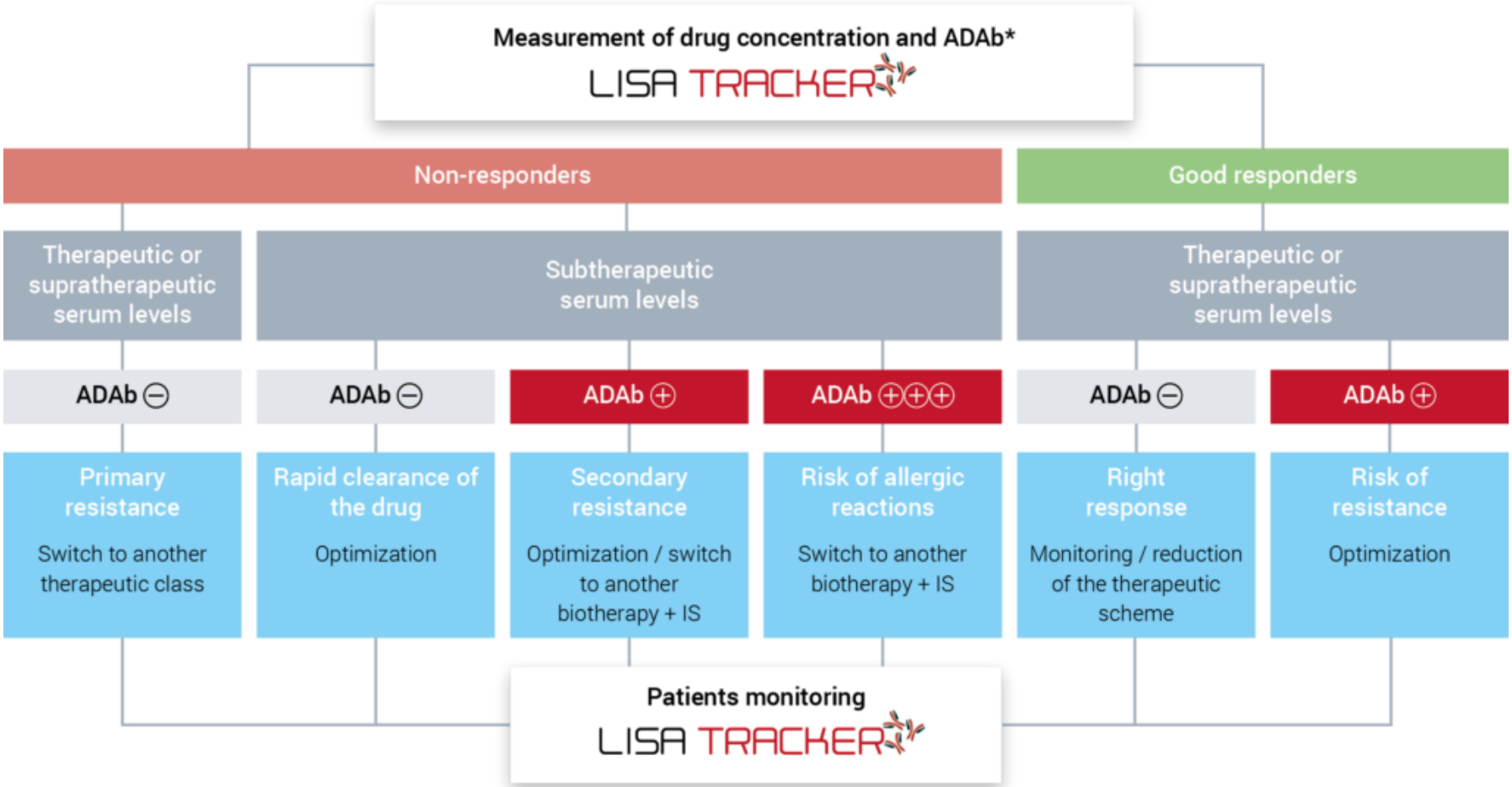
Anna Jamnitski [1], Geertje M Bartelds, Michael T Nurmohamed, Pauline A van Schouwenburg, Dirkjan van Schaardenburg, Steven O Stapel, Ben A C Dijkmans, Lucien Aarden, Gerrit Jan Wolbink

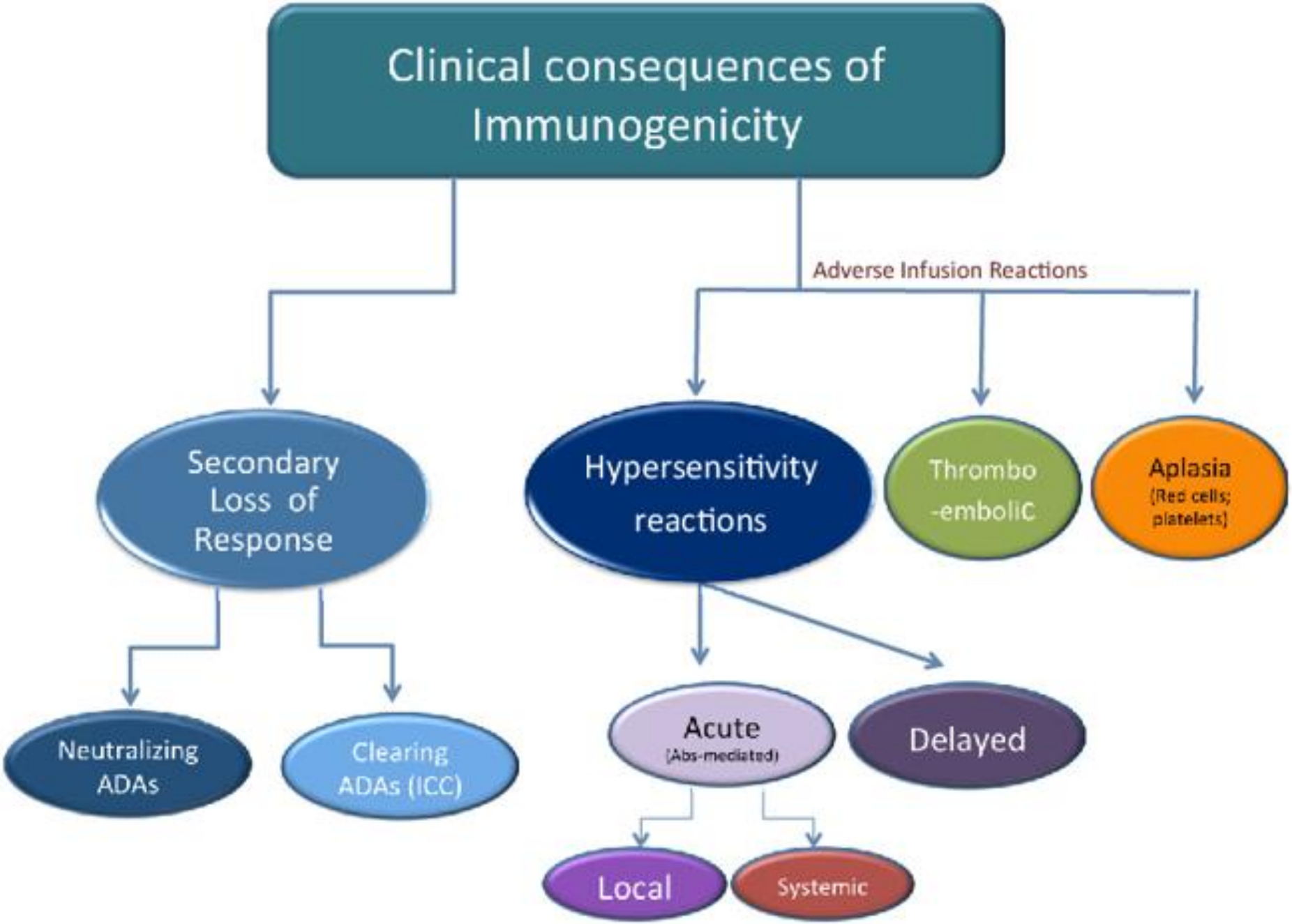
- Cohort study, 292 RA patients, all treated with etanercept.
- 89 patients (30%) were treated previously with infliximab or adalimumab ('switchers'), and the remaining 203 (70%) were anti-TNF naive.
- All switchers were divided into two groups: with and without antibodies against the previous biological.

- **Results:**
- After 28 weeks of treatment, response to etanercept did not differ between patients who were anti-TNF naive and switchers with anti-drug antibodies (ΔDAS28=2.1 ± 1.3 vs ΔDAS28=2.0 ± 1.3; p = 0.743).
- In contrast, switchers without anti-drug antibodies had a diminished response to etanercept treatment compared to patients who were TNF naive (ΔDAS28 =1.2±1.3 vs ΔDAS28 = 2.1 ± 1.3; p = 0.001) and switchers with antibodies (ΔDAS28 =1.2±1.3 vs ΔDAS28 = 2.0 ± 1.3; p = 0.017).

- Patients with RA with an immunogenic response against a first TNF-blocking agent had a better clinical response to a subsequent TNF blocker compared to patients with RA without anti-drug antibodies.

Ann Rheum Dis. 2011 Feb;70(2):284-8.


Measurement of drug concentration and ADAb*
LISA TRACKER
Non-responders
Good responders
Therapeutic or supratherapeutic serum levels
Subtherapeutic serum levels
Therapeutic or supratherapeutic serum levels
ADAb ⊖
ADAb ⊖
ADAb ⊕
ADAb ⊕⊕⊕
ADAb ⊖
ADAb ⊕
Primary resistance
Switch to another therapeutic class
Rapid clearance of the drug
Optimization
Secondary resistance
Optimization / switch to another biotherapy + IS
Risk of allergic reactions
Switch to another biotherapy + IS
Right response
Monitoring / reduction of the therapeutic scheme
Risk of resistance
Optimization
Patients monitoring
LISA TRACKER


Clinical consequences of Immunogenicity
Adverse Infusion Reactions
Secondary Loss of Response
Hypersensitivity reactions
Thrombo -embolic
Aplasia (Red cells; platelets)
Neutralizing ADAs
Clearing ADAs (ICC)
Acute (Abs-mediated)
Delayed
Local
Systemic