1) ΣΥΝΔΥΑΣΜΟΣ….ΜΤΧ+ «Βιολογικοί»(οφέλη) VS ΜΟΝΟΘΕΡΑΠΕΙΑ… με «Βιολογικούς»

2) ΑΝΟΣΟΓΟΝΙΚΟΤΗΤΑ «Βιολογικών»-οφέλη συγχορήγησης με ΜΤΧ

Ανδρέας Γ. Μπούνας

MTX

- Weinblatt et al 1984

Weinblatt ME, Coblyn JS, Fox DA, et al.
Efficacy of low-dose methotrexate in rheumatoid arthritis.
N Engl J Med 1985; 312:818–822

- 1988 FDA approved

MTX

- “Anchor” drug

Pincus T, Yazici Y, Sokka T, *et al*.

Methotrexate as the “anchor drug” for the treatment of early rheumatoid arthritis.

Clin Exp Rheumatol 2003;**21**(Suppl 31):S178–85

MTX

- 1η Επιλογή

Visser K, Katchamart W, Loza E, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E initiative. (Evidence-based recommendations on the clinical use of MTX)

Ann Rheum Dis 2008

Cécile Gaujoux-Viala, Josef S Smolen et al. Extended report: Current evidence for the management of rheumatoid arthritis with synthetic disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis.

Ann Rheum Dis 2010;69:1004-1009

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs

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Accepted 3 February 2010
JSS and RL are joint first

ABSTRACT
Treatment of rheumatoid arthritis (RA) may differ among rheumatologists and currently, clear and consensual international recommendations on RA treatment are not available. In this paper recommendations for the treatment of RA with synthetic and biological disease-modifying antirheumatic drugs (DMARDs) and glucocorticoids (GCs) that also account for strategic algorithms and deal with economic aspects, are described. The recommendations are based on evidence from five systematic literature reviews (SLRs) performed for synthetic DMARDs, biological DMARDs, GCs, treatment strategies and economic issues. The SLR derived evidence was discussed and

during the past decade, providing previously unforeseen therapeutic dimensions. New and highly effective DMARDs have continued to emerge until the most recent years—in particular, biological agents which target tumour necrosis factor, the interleukin 1 (IL-1) receptor, the IL-6 receptor, B lymphocytes and T-cell costimulation.[1] In addition, a chemical DMARD, leflunomide, has become available and compounds which have been in use for many decades, such as methotrexate (MTX) and sulfasalazine (SSZ), as well as GCs, have been re-examined in order to achieve better efficacy. For example, the use of high dose MTX[2] and the disease-modifying effects of GCs, especially when

Final set of 15 recommendations for the management of RA	
1	Treatment with synthetic DMARDs should be started as soon as the diagnosis of RA is made
2	Treatment should be aimed at reaching a target of remission or low disease activity as soon as possible in every patient; as long as the target has not been reached, treatment should be adjusted by frequent (every 1–3 months) and strict monitoring
3	MTX should be part of the first treatment strategy in patients with active RA
4	When MTX contraindications (or intolerance) are present, the following DMARDs should be considered as part of the (first) treatment strategy: leflunomide, SSZ or injectable gold

Ρευματολόγοι και MTX σαν πρώτη επιλογή στην PA

	Φιλανδία	**Nashville**
1980	*<5%*	*<25%*
2004	*90%*	*90%*

Efficacy of methotrexate in comparison to biologics in rheumatoid arthritis

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Key words: Methotrexate, biologics, rheumatoid arthritis

ABSTRACT

This paper reviews trials comparing the efficacy of MTX and biologic agents. So far, the clinical evaluations of 9 biologics have been published. Three TNF inhibitors – etanercept, adalimumab, golimumab – and the IL 6 receptor inhibitor tocilizumab have been investigated in MTX naïve patients using a parallel design. The trials had 3 treatment arms: monotherapies of MTX and of the biologic compound, and the combination of both. The other biologics – infliximab, certolizumab pegol, anakinra, rituximab, and abatacept mechanism of action. Nonetheless, all trials confirmed a surprisingly good performance of MTX in comparison with biologics.

Introduction

This paper reviews trials comparing the efficacy of MTX with that of biologics in the treatment of rheumatoid arthritis. So far, nine biologics have been clinically evaluated in RA and are included in this overview. These are five TNF-α inhibitors, one IL 1 receptor antagonist, one IL 6 receptor inhibitor, one CD20+ B-cell inhibitor and one costimulation

MTX vs «Βιολογικοί»

- Σε MTX«naïve» ασθενείς…ΑΜΕΣΗ σύγκριση μόνο τα:

  Etanercept
  Adalimumab
  Golimumab

  Tocilizumab

ΓΕΝΙΚΑ…

- Παρόμοια αποτελεσματικότητα κατά ACR,EULAR
- Παρόμοια ποσοστά ύφεσης
- Ταχύτερη έναρξη δράσης οι «ΒΙΟΛΟΓΙΚΟΙ»
- Καθυστερούν περισσότερο την ακτινολογική εξέλιξη

Φαίνεται …

- MTX ελαφρά ανώτερη από Adalimumab
- ισοδύναμη με Golimumab,ETA
- σαφώς κατώτερη του Tocilizumab

επίσης…

- Και η MTX είχε (-) ακτινολογικά scores…(Επούλωση)

- TEMPO:στα 3 έτη μέση επιδείνωση(κατά Sharp score)
  MTX 1.2 %
  etanercept(ETA) 0.4
  (επί συνόλου 448 units)

- με probability plot(ITT) ποσοστό ασθενών με επιδείνωση στην 3ετία
  MTX 20%
  ETA 15%

ΟΜΩΣ…

- Σημαντική ενίσχυση δράσης «BIO» με προσθήκη MTX !

  - μείωση ενεργότητας(ACR,EULAR)

  - μείωση ακτινολογικής εξελιξης

Μελέτη ERA (…naïve ασθενείς σε MTX-early RA)

- Σε 12 μήνες ACR 20 (ποσοστό ασθενών)

MTX 65 %

ETA 72 %

(p=0.16) !!!

Μελέτη ERA

- Σε 24μήνες ΌΧΙ αύξηση Sharp score (ποσοστό ασθενών)

MTX	51 %
ETA	63 %

Μελέτη TEMPO

- 686 pts (42% nonresponders MTX)
- Active RA (6.7 yrs)
- ETA MTX ETA+MTX

Μελέτη TEMPO
(απάντηση ασθενών % ACR50)

	MTX	ETA	MTX+ETA
Year 1	43	48	69
Year 2	42	54	71
Year 3	44	46	61

years were not significantly different between both monotherapies but were significantly greater in the combination group (Table I).

Within the MTX group, the proportion of patients in clinical remission at 3 years was nearly doubled using the completer analysis *versus* the ITT analysis with LOCF, while in the etanercept and combination groups the difference between both analyses was only 30% and 20%, respectively (Table II): more patients were withdrawn with MTX and therefore had less time to improve with treatment.

The mean radiographic progression over three years as measured with the Sharp total score was 5.95 in the MTX group, 1.61 in the etanercept group, and -0.14 (95% CI -1.07, 0.78) in the combination group. Again, the difference between combination or continued MTX treatment. As a result, patients treated with the was increased in 11% of the combination and 25% of the adalimumab mono-

Table I. Tempo trial: ACR responses (% of patients) over three years.

	MTX			Etanercept			Combination		
ACR response	20 %	50 %	70 %	20 %	50 %	70 %	20%	50%	70%
Year 1	75	43	19	76	48	24	85	69	43
Year 2	71	42	21	75	54	27	86	71	49
Year 3	70	44	21	71	46	26	85	61	42

Table II. Tempo trial: DAS 28 Remissions (% of patients) over 3 years.

	ITT (LOCF) analysis			Completer analysis		
DAS28 <2.6	MTX	Etanerc.	Etan. + MTX	MTX	Etan.	Etan. + MTX
Year 1	17.1	17.5	38.1*#	21.8	22.0	43.2*#
Year 2	18.9	22.4	42.4*#	25.6	29.6	53.7*#
Year 3	18.9	20.6	40.3*#	36.0	30.8	51.5#

*$p<0.01$ *vs.* MTX.
#$p<0.01$ *vs.* etanercept.

Μελέτη TEMPO
(απάντηση ασθενών % ACR50)

	MTX	ETA	MTX+ETA
Year 1	43	48	69
Year 2	42	54	71
Year 3	44	46	61

Μελέτη TEMPO
(απάντηση ασθενών % ACR70)

	MTX	ETA	MTX+ETA
Year 1	19	24	43
Year 2	21	27	49
Year 3	21	26	42

Μελέτη TEMPO

(απάντηση ασθενών % DAS28<2.6)

	MTX	ETA	MTX+ETA
Year 1	17	17	38
Year 2	19	22	42
Year 3	19	20	40

Μελέτη TEMPO

(ποσοστό ασθενών με ακτινολογική ύφεση μετά 3ετή αγωγή)

MTX	ETA	MTX+ETA
51%	61%	76%*

*(p=0.05)

Μελέτη PREMIER

- 799 MTX naïve pts
- Early RA (0.6-0.7yrs)
- ADA MTX ADA+MTX

Μελέτη PREMIER
(απάντηση ασθενών % ACR50)

	MTX	ADA	MTX+ADA
Year 1	46	41	62*

*(p=0.001)

Μελέτη PREMIER
(απάντηση ασθενών % DAS28<2.6)

	MTX	ADA	MTX+ADA
Year 2	25	25	49*

*(p=0.001)

Μελέτη PREMIER

(ποσοστό ασθενών με ακτινολογική ύφεση μετά 2ετή αγωγή)

MTX	ADA	MTX+ADA
34%	45%*	61%**

*(p=0.001)

**(p=0.001)

Ομως στις μελέτες….

- Χαμηλές δόσεις MTX(7.5mg) αρχικά

- «Αδικίες» κατά τις στατιστικές αναλύσεις λόγω περισσοτέρων dropouts στις ομάδες MTX

  - καί για ενεργότητα νόσου

  -καί για ακτινολογική εξέλιξη

- Δόσεις φυλλικού οξέως(μείωση ενεργότητας)

MTX

Gold Standard

Πιο αποτελεσματικές

- Υψηλές δόσεις
- Διηρημένες δόσεις
- Παρεντερική χορήγηση (early)

MTX

- Έναρξη 15mg/εβδ (per os κ΄ split)
- Μέχρι 25 – 30 mg/εβδ (↑5mg κάθε μήνα)
- Switch σε υποδόρια (νωρίς)

ΑΝΟΣΟΓΟΝΙΚΟΤΗΤΑ

(Immunogenicity)

ΑΝΟΣΟΓΟΝΙΚΟΤΗΤΑ **(Immunogenicity)**

- ….Αντισώματα έναντι συγκεκριμένων φαρμάκων…(Πρωτεϊνικης δομής)

- «Βιολογικοί» - “Biologicals”

“ BIOLOGICALs”

- Φάρμακα – προϊόντα Βιοτεχνολογίας
- Φυσικές πρωτείνες
  - Ορμόνες
  - Κυτταροκίνες
  - Αυξητικοί παράγοντες
- Κατασκευασμένα μόρια
  - Αντισώματα
  - Τμήματα αντισωμάτων
  - Πρωτεϊνικές δομές

- 30 τουλάχιστον αντισώματα και παράγωγα αντισωμάτων…”Approved”

- 9 Βιολογικοί σήμερα στην RA

  6 μονοκλωνικά αντισώματα

  2 fusion proteins(ABT,ETA)

Διαφορές ανοσοαπάντησης…

- έναντι “native biologicals”
- καί έναντι “designed biologicals”

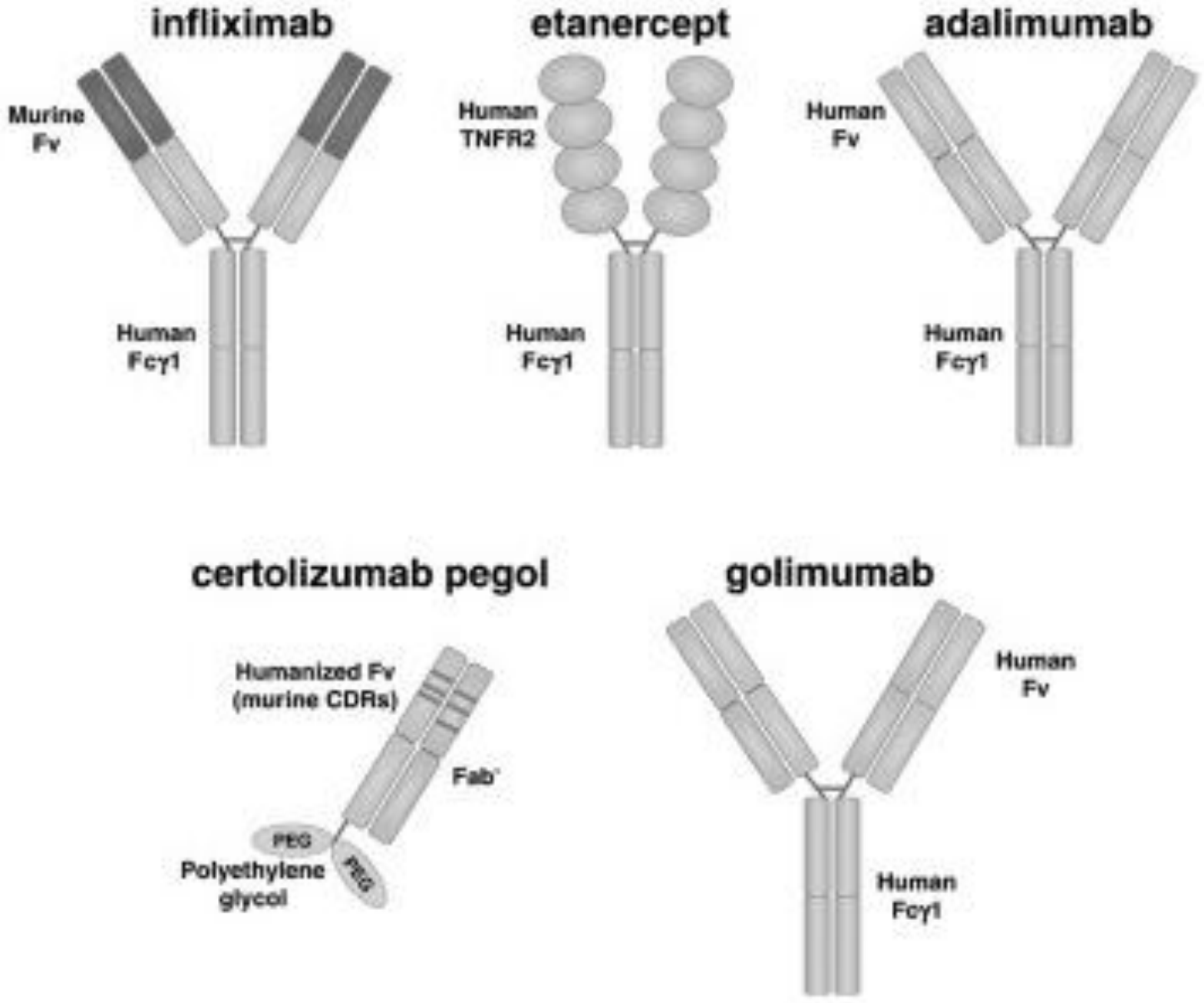
ΒΙΟΛΟΓΙΚΟΙ

- (Μιμούνται χορήγηση …εμβολίων)

- Δυνητικά όλοι οι βιολογικοί επάγουν ΑΝΟΣΟΓΟΝΙΚΟΤΗΤΑ

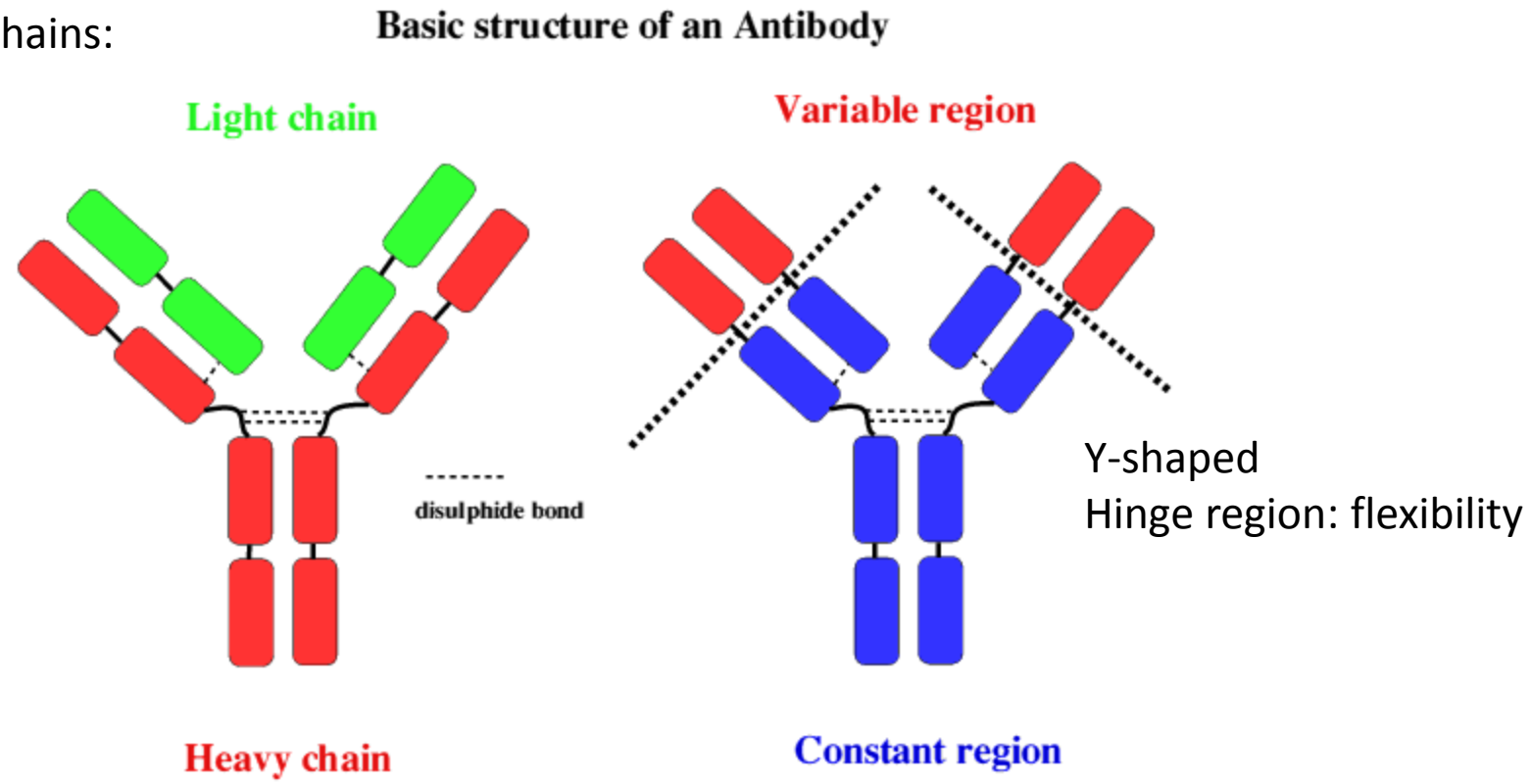
- (Σπανιότερα οι native,αλλά…πχ ερυθροποιητίνη...)

- **HAMA** (Human Anti-Mouse Antibodies)
- **HACA** (Human Anti-Chimeric Antibodies)
- **HAHA** (Human Anti-Human Antibodies)


infliximab
Murine Fv
Human Fcγ1
etanercept
Human TNFR2
Human Fcγ1
adalimumab
Human Fv
Human Fcγ1
certolizumab pegol
Humanized Fv (murine CDRs)
Fab'
PEG
PEG
Polyethylene glycol
golimumab
Human Fv
Human Fcγ1

Light Chains:

1. κ
2. λ



Y-shaped

Hinge region: flexibility

Heavy Chains:

1. α (IgA)
2. δ (IgD)
3. ε (IgE)
4. γ (IgG)
5. μ (IgM)

IgG subclasses:

IgG_1

IgG_2

IgG_3

IgG_4

Anti-TmAb

(Αντισώματα έναντι θεραπευτικών μονοκλωνικών αντισωμάτων)

Συνήθως…

- **Αντι-ιδιοτυπικά**

Και επομένως…

- **Neutralizing** (Εξουδετερωτικά)

Επίπτωση ανοσογονικότητας…

- Σε αποτελεσματικότητα

  (Θεραπευτική αστοχία)

- Σε ασφάλεια

  (Αλλεργικές αντιδράσεις)

Αλλεργικές αντιδράσεις

- Οξείες…**anaphylaxis**

  IgE-mediated τύπου **I**

- Πιο όψιμες…

  IC-mediated τύπου **III**

Αλλεργικές αντιδράσεις

- Περισσότερες…. σε ασθενείς με υψηλότερα επίπεδα ATIs (με ν.Crohn)

Baert. NEJM 2003

- Ποσότητα και ποιότητα IC καθορίζουν την αντίδραση

van der Laken ARD 2007

Dealing with immunogenicity of biologicals: assessment and clinical relevance

Gerrit J. Wolbink[a,b], Lucien A. Aarden[b] and B.A.C. Dijkmans[a,c]

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Current Opinion in Rheumatology 2009, 21:211–215

Purpose of review

In the last decade, biologicals revolutionized rheumatology. An increasing number of patients benefit from biotherapeuticals. However, some patients do not respond to treatment and others lose their response after a certain time. Immunogenicity is one of the factors linked to secondary nonresponse but its clinical significance has remained controversial.

Recent findings

In recent years, knowledge of how to assess immunogenicity of biologicals has improved. Various reports show an inverse relationship between drug levels and antibody formation against the drug. Studies associated immunogenicity of therapeutic antibodies with clinically significant nonresponse in a subgroup of patients. Clinically relevant immunogenicity is influenced by several factors including dosing and concomitant medication. It has been shown that immunogenicity against biologicals can be persistent or transient.

Summary

Assessing immunogenicity… **(μέθοδος)**

- ELISA
- Two-site (bridging) assay
- Antigen binding test (RIA)

Assessing immunogenicity… **(timing) 1**

- Half-life anti-IgG……3 εβδ
- Half-life IC…….πολύ μικρότερη
- Σχέση ποσότητας Ag-Ab

Clinical response and pharmacokinetics

- Χορήγηση μιάς δόσης infliximab –v.Crohn
- HACAs σε 61% ασθενών
- Σημαντική μείωση ποσοστού…συνεχίζοντας τις εγχύσεις
- Περαιτέρω μείωση συγχορηγόντας MTX ή AZA

Baert F. NEJM 2003

Antiinfliximab (ATIs) σε RA

- Δόση 10 mg/kg……ATIs 7% ασθενών
- Δόση 3 mg/kg……ATIs 21% ασθενών
- Δόση 1 mg/kg……ATIs 53% ασθενών

- Περαιτέρω μείωση με συγχορήγηση MTX (0%,7%,15%)

Maini A&R 1998

Maini A&R 2004

Anti-TmAb
(Αντισώματα έναντι θεραπευτικών μονοκλωνικών αντισωμάτων)

- Η συγχορήγηση MTX μειώνει την παραγωγή τους μέσω…

  -ανοσοκαταστολής

  -ανοσοανοχής

Η συγχορήγηση ΜΤΧ…

- Αυξάνει τα επίπεδα π.χ infliximab σε RA και ν.Crohn λόγω...

  - **ανοσοκαταστολής**
  - **ανοσοανοχής**
  - **μείωσης παραγωγής TNFα**

EXTENDED REPORT

Relationship between serum trough infliximab levels, pretreatment C reactive protein levels, and clinical response to infliximab treatment in patients with rheumatoid arthritis

G J Wolbink, A E Voskuyl, W F Lems, E de Groot, M T Nurmohamed, P P Tak, B A C Dijkmans, L Aarden

Ann Rheum Dis 2005;**64**:704–707. doi: 10.1136/ard.2004.030452

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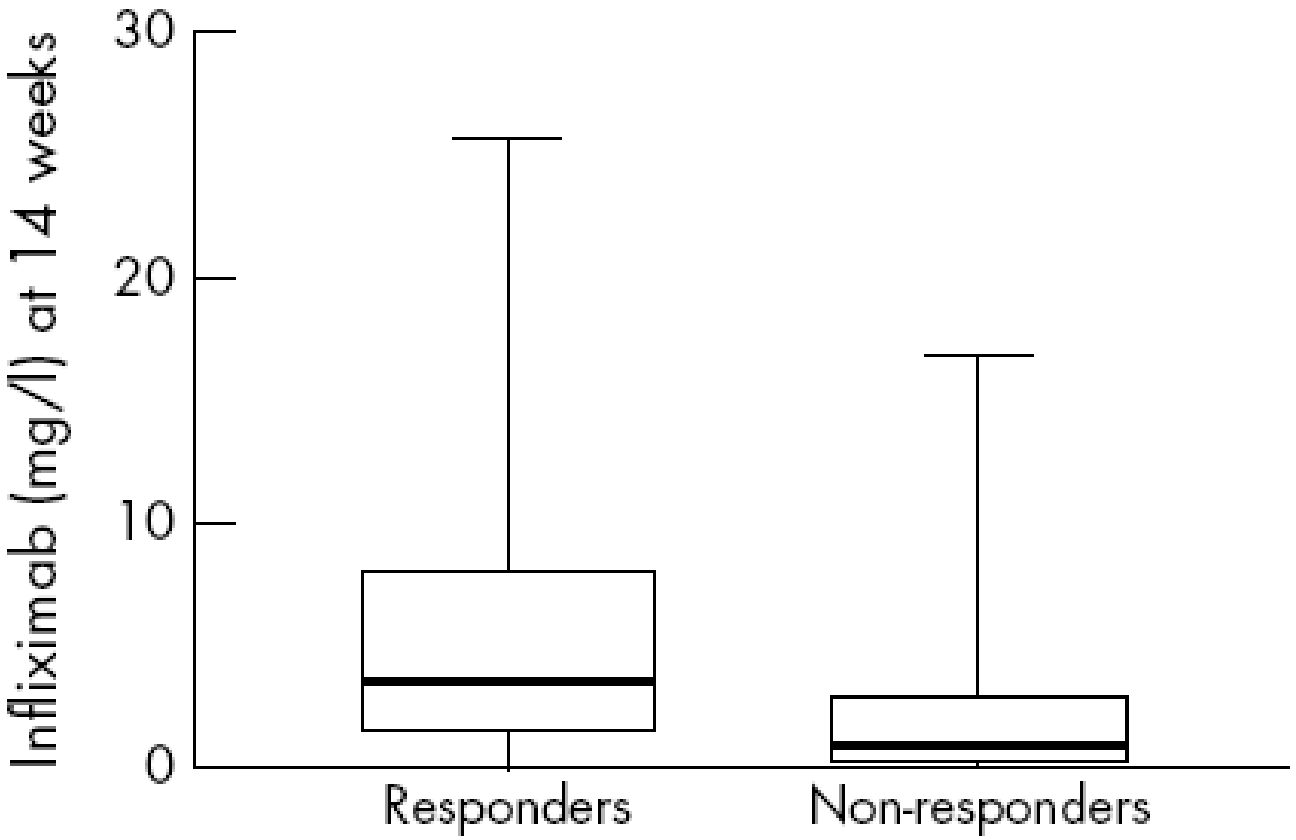
Objective: To investigate the relationship between serum trough infliximab levels and clinical response to infliximab treatment in patients with rheumatoid arthritis (RA).
Methods: Disease activity and serum trough infliximab levels before and 2, 6, and 14 weeks after initiation of infliximab treatment at a dose of 3 mg/kg in a cohort of 105 patients with RA were assessed. Serum trough infliximab levels in responders and non-responders were compared. Additionally, the clinical responses of patients with high, intermediate, and low serum trough infliximab levels at 14 weeks were compared.
Results: After 14 weeks of treatment non-responders had lower serum trough levels of infliximab than responders (median (interquartile range) 0.5 (0.2–2.2) *v* 3.6 (1.4–8.2) mg/l; $p<0.01$)). Patients with low serum trough infliximab levels at 14 weeks had significantly less improvement in the 28 joint count Disease Activity Score (DAS28) score than patients with intermediate or high serum trough infliximab levels at 14 weeks. Pretreatment C reactive protein (CRP) levels correlated negatively with serum trough infliximab levels at 14 weeks after the start of treatment (Spearman rank correlation $r_s = -0.43$, $p<0.001$).
Conclusion: Serum trough levels of infliximab correlate with the clinical response to treatment with infliximab and pretreatment CRP levels. This study indicates that patients with high pretreatment CRP levels might benefit from higher dosages of infliximab or shorter dosing intervals.

The efficacy of infliximab as a treatment for patients with

observational study. Patients were enrolled at the depart-


Infliximab (mg/l) at 14 weeks
30
20
10
0
Responders
Non-responders

ARTHRITIS & RHEUMATISM
Vol. 54, No. 3, March 2006, pp 711–715
DOI 10.1002/art.21671

Development of Antiinfliximab Antibodies and Relationship to Clinical Response in Patients With Rheumatoid Arthritis

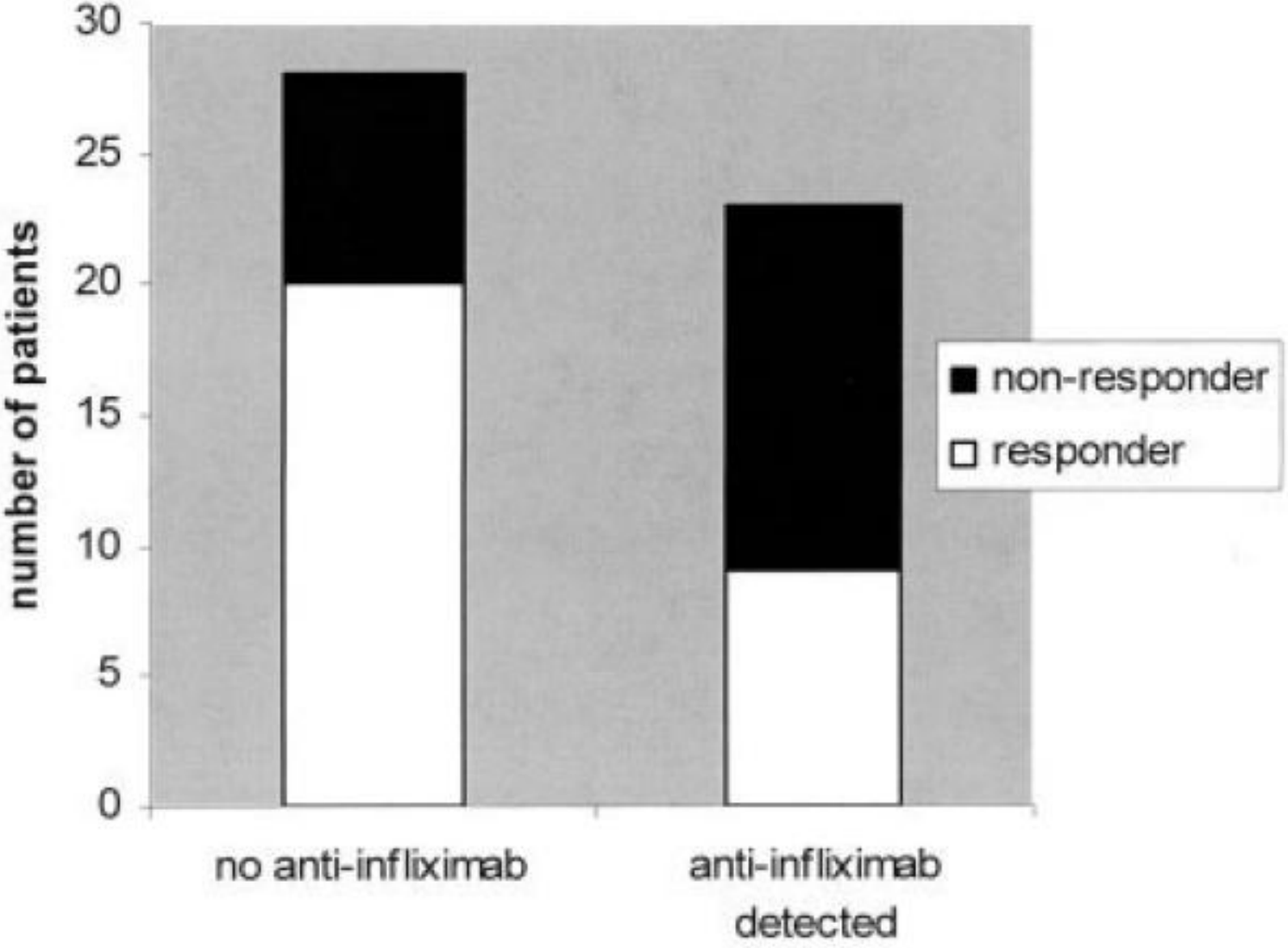
Gerrit Jan Wolbink,[1] Marijn Vis,[2] Willem Lems,[2] Alexandre E. Voskuyl,[3] Els de Groot,[4] Michael T. Nurmohamed,[5] Steven Stapel,[4] Paul P. Tak,[6] Lucien Aarden,[4] and Ben Dijkmans[3]

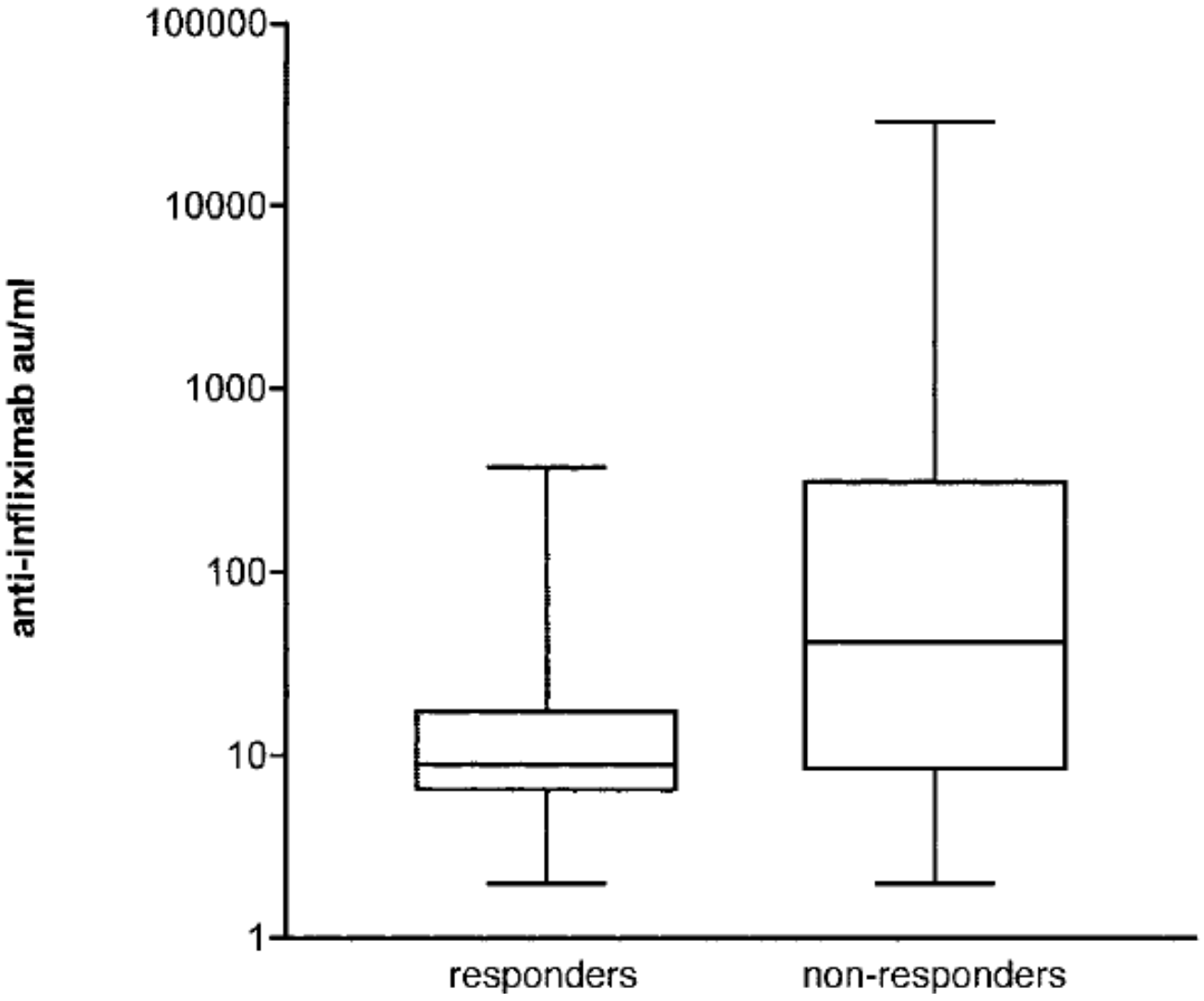
***Objective.* Treatment of patients with infliximab, a chimeric monoclonal IgG1 antibody against tumor necrosis factor, may result in the formation of infliximab-specific IgG antibodies. This study evaluated the clinical significance of these antibodies in patients with rheumatoid arthritis (RA).**

***Methods.* Antiinfliximab antibodies were measured using a newly developed radioimmunoassay in a cohort of 51 consecutive patients with RA treated with infliximab, with a followup of 1 year. In addition, serum infliximab levels were determined by enzyme-linked immunosorbent assay. The results were analyzed in relation to the clinical response to treatment according to the European League Against Rheumatism criteria.**

***Results.* Antibodies against infliximab were de- imab antibodies within the first year of treatment. This seems to be clinically relevant, since development of antiinfliximab antibodies is associated with a reduced response to treatment.**

Treatment with infliximab provides great benefit to many patients with rheumatoid arthritis (RA) (1–3). However, some patients have persistent active disease and others show loss of efficacy after prolonged treatment. Infliximab can induce the formation of antibodies to infliximab that may lead to side effects and loss of efficacy. Development of antibodies to infliximab is related to the dose of infliximab and is diminished by concomitant treatment with methotrexate (MTX) (1). To what extent formation of antibodies to infliximab


30
25
20
15
10
5
0
number of patients
non-responder
responder
no anti-infliximab
anti-infliximab detected


anti-infliximab au/ml
100000
10000
1000
100
10
1
responders
non-responders

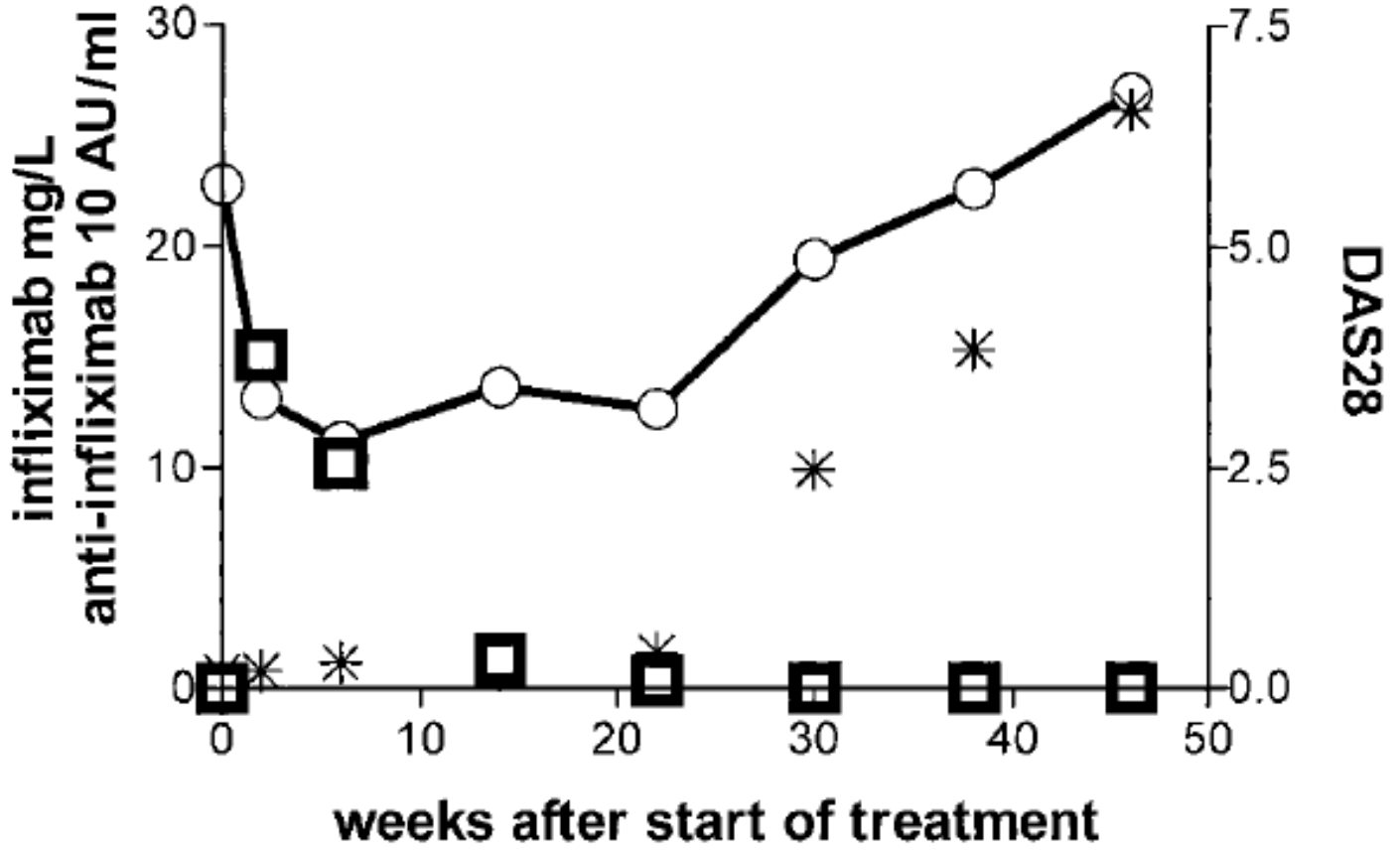


Figure 3. Trough levels of infliximab in the serum (□), levels of antiinfliximab (∗), and the Disease Activity Score in 28 joints (DAS28) (○) in a rheumatoid arthritis patient treated with infliximab. After an initial improvement of disease activity, the patient had a relapse of disease activity that coincided with a decrease in the serum trough levels of infliximab and an increase in the antiinfliximab titer. AU = arbitrary units.

Antiinfliximab (ATIs)σε RA

- Στις 52εβδ …22 ασθενείς(43%)
  - χαμηλό infliximab
  - υψηλά ATIs
- 3 (από τους 22) infusion reactions
- ATIs συχνότερα σε non-responders (p=0.04)
- Επίπεδα infliximab:
  - risponders 12,7 mg/l
  - non-risponders 0.02 mg/l

Vries,Wolbink ARD 2007

CONCISE REPORT

Decreased clinical response to infliximab in ankylosing spondylitis is correlated with anti-infliximab formation

Mirjam K de Vries, Gerrit Jan Wolbink, Steven O Stapel, Henk de Vrieze, J Christiaan van Denderen, Ben A C Dijkmans, Lucien A Aarden, Irene E van der Horst-Bruinsma

Ann Rheum Dis 2007;**66**:1252–1254. doi: 10.1136/ard.2007.072397

Objectives: Correlation of serum trough infliximab levels and antibodies to infliximab (anti-infliximab) with clinical response in ankylosing spondylitis.

Methods: In accordance with the international ASsessment in Ankylosing Spondylitis (ASAS) consensus statement, patients were treated with infliximab (5 mg/kg) every 6 weeks after a starting regimen. Preinfusion sera were collected at baseline, 24 and 54 weeks. At every visit, the 20% improvement response (ASAS-20) was assessed and laboratory tests performed.

Results: 24 of the 38 (63%) patients fulfilled ASAS-20 response criteria after 24 weeks of treatment and 21 (53%) after 54 weeks. After 54 weeks, 11 (29%) patients showed undetectable serum trough infliximab levels and detectable anti-infliximab; six of these patients developed an infusion reaction. Anti-infliximab was found significantly more often ($p = 0.04$) in ASAS-20 non-responders compared with responders at week 54. Serum trough infliximab levels were significantly ($p<0.0001$) lower in patients with (mean 0.02 mg/l) than in those without (12.7 mg/l) anti-infliximab.

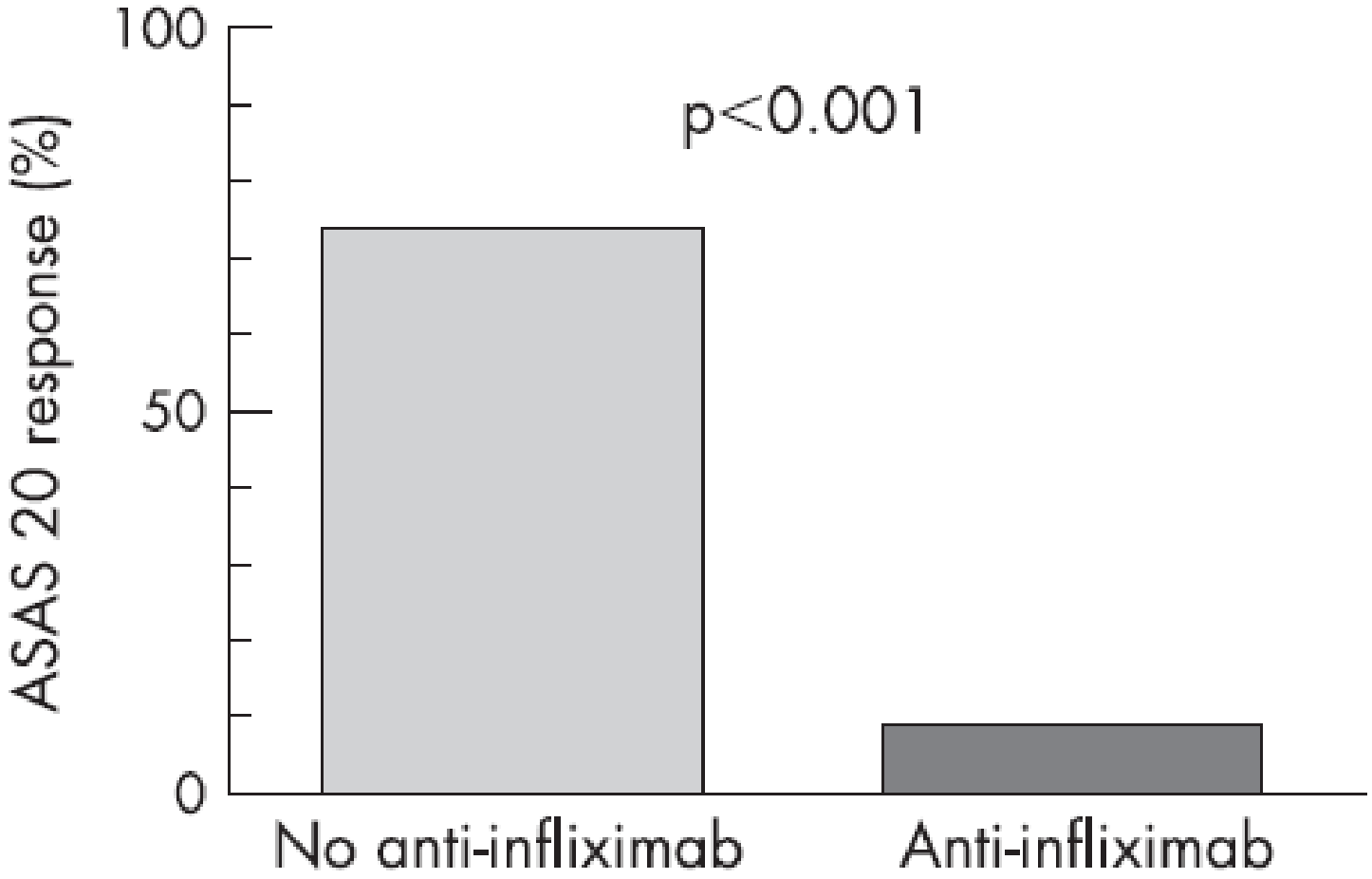
Conclusions: In ankylosing spondylitis, high levels of serum trough infliximab correlated with a good clinical response.

Disease activity was measured with the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[8] and the ASsessment in Ankylosing Spondylitis 20% response criteria (ASAS-20).[9] Active disease was defined as a BASDAI score $\geqslant 4$. Response to treatment with infliximab was defined as fulfilment of the ASAS-20 response criteria.

Patients with ankylosing spondylitis were treated with intravenous infliximab, 5 mg/kg bodyweight at baseline, weeks 2 and 6, and every 6 weeks thereafter. This treatment was initiated in accordance with the international ASAS consensus statement.[9] In case of decrease of clinical response, the dose of infliximab was increased to 7.5 mg/kg.

At each visit, the presence of infections, side-effects or infusion reactions, and the cause for discontinuation of therapy were recorded. Questionnaires and routine laboratory tests were obtained. Preinfusion sera were collected at baseline, weeks 24 and 54, before any dose escalation and at two consecutive visits after dose escalation. After 24 weeks of treatment, serum samples were collected from 15 patients to measure infliximab levels 2 weeks after the infliximab infusion.

Validated immunoassays (Sanquin Research, Amsterdam, the Netherlands) were used for detection of anti-infliximab and serum trough infliximab levels.[5] Trough serum infliximab levels were measured by ELISA, based on the principle that infliximab is


100
50
0
ASAS 20 response (%)
p<0.001
No anti-infliximab
Anti-infliximab

Antiinfliximab (ATIs)σε AS

- Στις 54 εβδ …11 ασθενείς(29%)
  - χαμηλό infliximab
  - υψηλά ATIs
- 6 (από τους 11) infusion reactions
- ATIs συχνότερα σε non-responders (p=0.04)
- Επίπεδα infliximab:
  - responders 12,7 mg/l
  - non-responders 0.02 mg/l

EXTENDED REPORT

Clinical response to adalimumab: relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis

Geertje M Bartelds, Carla A Wijbrandts, Michael T Nurmohamed, Steven Stapel, Willem F Lems, Lucien Aarden, Ben A C Dijkmans, Paul Peter Tak, Gerrit Jan Wolbink

Ann Rheum Dis 2007;**66**:921–926. doi: 10.1136/ard.2006.065615

See end of article for authors' affiliations

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Accepted 4 February 2007
Published Online First 14 February 2007

Background: A substantial proportion of patients with rheumatoid arthritis (RA) do not respond, or lose initial response, to adalimumab treatment. One explanation for non-response is that patients develop anti-adalimumab antibodies.

Objectives: To evaluate the incidence of formation of antibody against adalimumab and the association with serum adalimumab concentrations and clinical response.

Methods: In a cohort of 121 consecutive patients with RA treated with adalimumab, serum adalimumab concentrations and antibodies against adalimumab were measured together with clinical response variables before and up to 28 weeks after the start of treatment.

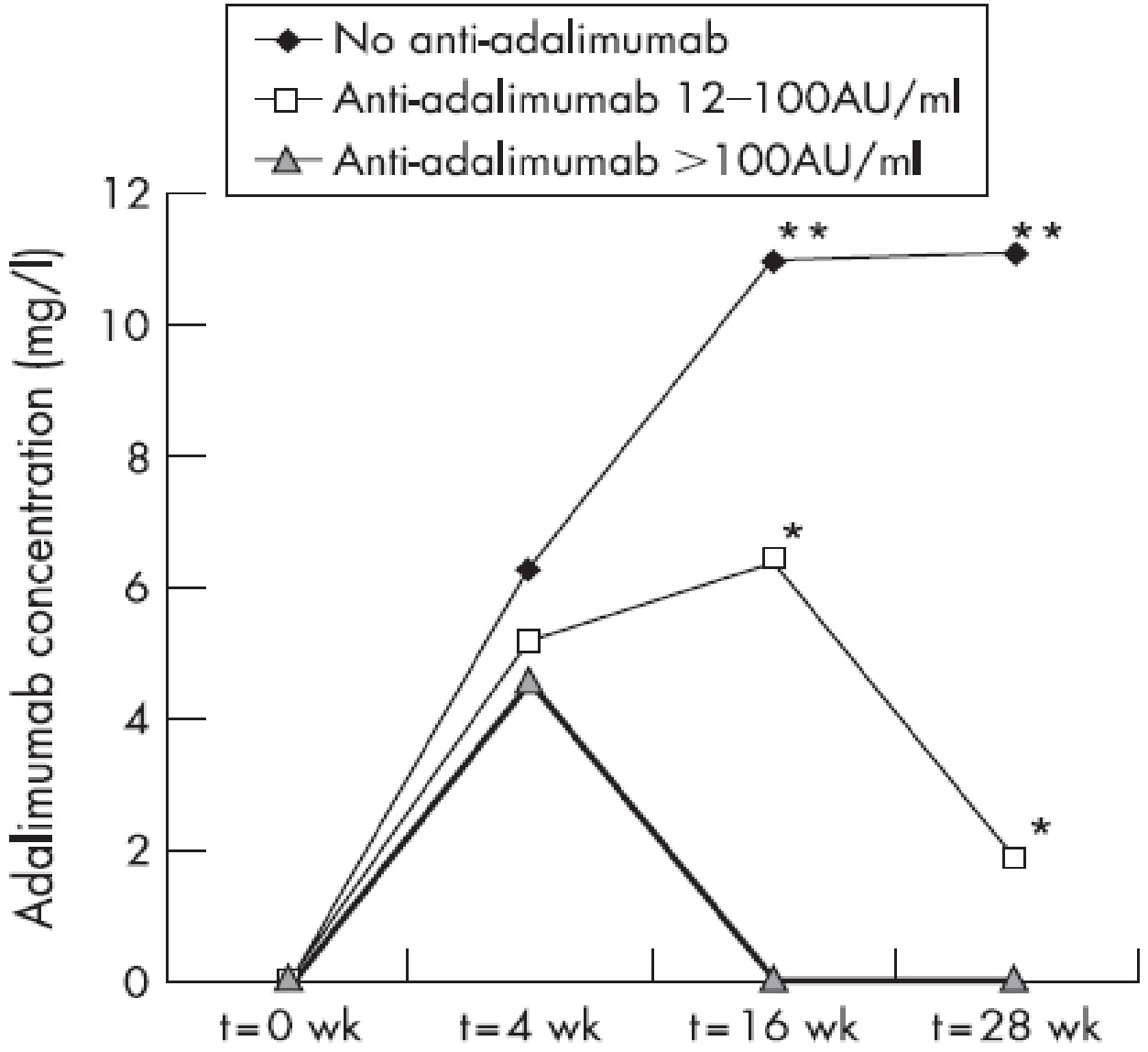
Results: Anti-adalimumab antibodies were detected in 21 patients (17%) during 28 weeks of treatment. EULAR non-responders had antibodies significantly more often than good responders (34% vs 5%; $p = 0.032$). Patients with antibodies showed less improvement in disease activity (mean (SD) delta DAS28 0.65 (1.35)) than patients without antibodies (mean delta DAS28 1.70 (1.35)) ($p = 0.001$). Patients with antibodies during follow-up had lower serum adalimumab concentrations at 28 weeks than patients without antibodies (median 1.2 mg/l, range 0.0–5.6 vs median 11.0 mg/l, range 2.0–33.0, respectively; $p<0.001$). Good responders had higher serum adalimumab concentrations than moderate responders ($p = 0.021$) and non-responders ($p = 0.001$). Concomitant methotrexate use was lower in the group with anti-adalimumab antibodies (52%) than in the group without antibodies (84%) ($p = 0.003$).

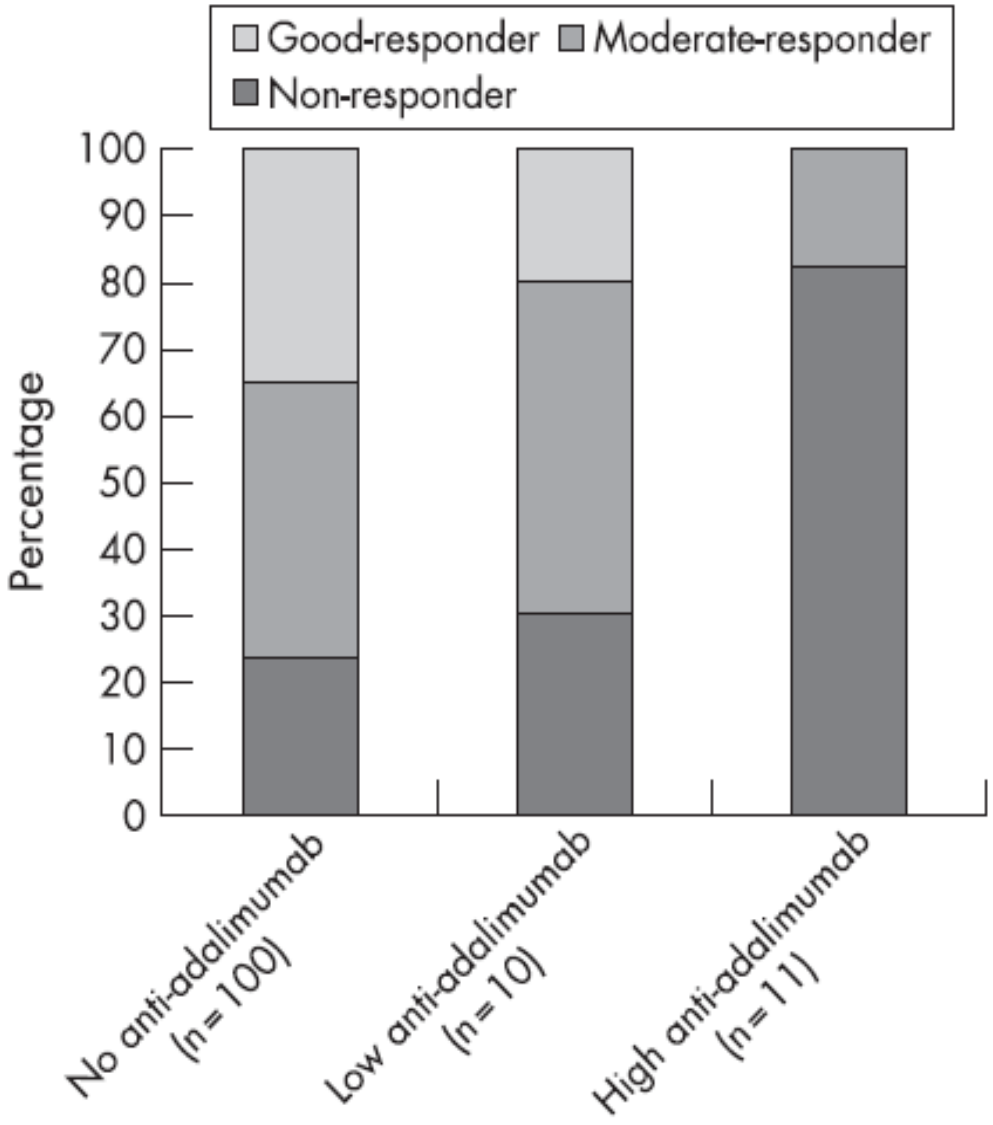
Conclusions: Serum antibodies against adalimumab are associated with lower serum adalimumab concentrations and non-response to adalimumab treatment.

Antiadalimumab (AAAs) σε RA

- Αγωγή 121 ασθενείς για 28 εβδ
- 21 ασθ (17%) είχαν AAAs
- AAAs: 34% των non-responders
  5% των responders
- Group AAAs(-) λήψη MTX 84%
  Group AAAS(+) λήψη MTX 52%

Bartelds ARD 2007


No anti-adalimumab
Anti-adalimumab 12–100AU/ml
Anti-adalimumab >100AU/ml
Adalimumab concentration (mg/l)
12
10
8
6
4
2
0
t=0 wk
t=4 wk
t=16 wk
t=28 wk
**
**
*
*


Good-responder
Moderate-responder
Non-responder
Percentage
100
90
80
70
60
50
40
30
20
10
0
No anti-adalimumab (n=100)
Low anti-adalimumab (n=10)
High anti-adalimumab (n=11)

AAAs σε ασθενείς με AS

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Decreased clinical response to adalimumab in ankylosing spondylitis is associated with antibody formation

Treatment with anti-tumour necrosis factor (TNF) is very effective in most patients with ankylosing spondylitis (AS), but inefficacy occurs in about 40% of cases.[1] Antibody formation against TNF blocking agents is an increasingly recognised problem;[2] however, no data have yet been reported on antibody formation against adalimumab (anti-adalimumab) in AS. Lack of response can be explained in two ways: (1) TNF might not be important for disease activity in certain patients; and (2) TNF inhibition might be insufficient. The latter could be caused by excessive production of TNF, low compliance of the patient, insufficient dosing or an enhanced clearance of adalimumab due to antibody formation. Adalimumab is a fully human monoclonal antibody against TNF but, despite this fact, an immune response still can be provoked by the antigen binding site also known as the idiotype. In previous studies we have described the problem of immunogenicity of TNF blocking drugs in patients with rheumatoid arthritis (RA),[3] in patients with AS treated with infliximab[4] and in patients with RA treated with adalimumab,[5] and concluded that the presence of antibodies against infliximab or adalimumab was associated with low or undetectable serum levels of infliximab or adalimumab and

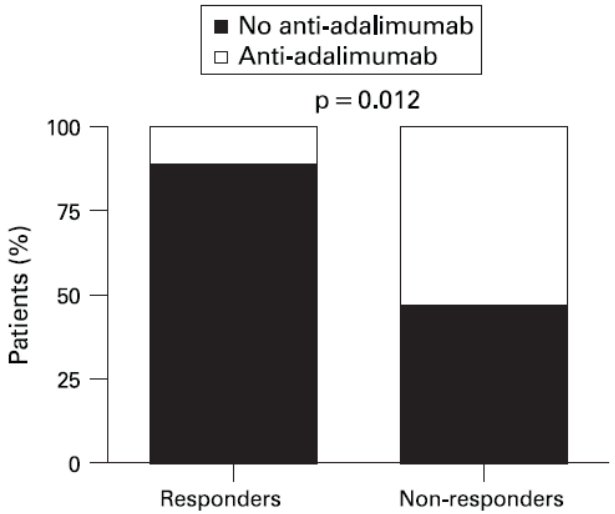

Figure 1 Relation between the presence of anti-adalimumab and response of ankylosing spondylitis to treatment with adalimumab.

adalimumab levels were determined with an ELISA and anti-adalimumab was measured with a validated antigen binding test. The assays used were similar to those described previously for the detection of infliximab levels and antibodies against infliximab.[4 5]

Thirty-five patients were included. After 6 months of treatment, 18 were ASAS responders (table 1). Within 6 months of treatment, 11 patients developed anti-adalimumab with low or undetectable adalimumab levels, 9 were ASAS non-responders ($p = 0.012$) and 1 had an allergic reaction with flushing,

Immunogenicity does not influence treatment with etanercept in patients with ankylosing spondylitis

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ABSTRACT

Background: Immunogenicity, specifically the onset of antibodies against tumour necrosis factor (TNF) blocking agents, seems to play an important role in non-response to treatment with these drugs.

Objectives: To assess the relation of clinical response of ankylosing spondylitis (AS) to etanercept with etanercept levels, and the presence of antibodies to etanercept.

Methods: Patients with AS were treated with etanercept 25 mg twice weekly, according to the international Assessment in Ankylosing Spondylitis (ASAS) working group consensus statement. Sera were collected at baseline and after 3 and 6 months of treatment. Clinical response was defined as a 50% improvement or as an absolute improvement of 2 points on a (0–10 scale) Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score. Functional etanercept levels were measured by a

this failure could be the formation of antibodies, which results in lower or undetectable serum levels of the biological agent.

For etanercept, however, it is unclear whether a relation between clinical response and the formation of antibodies is present in patients with AS. In addition, many questions concerning immunogenicity have not yet been answered and different methods of detection of anti-etanercept antibodies are being used, which makes the results difficult to compare.[5 6]

In our previous studies, we demonstrated a correlation between clinical response and serum trough infliximab levels, adalimumab levels and the onset of antibodies against these drugs.[7 8] In this study, we used the same approach as in our previous studies to investigate the relation

Antietanercept(AEAs) σε AS

- Αγωγή 12 εβδ σε 53 ασθενείς
- 76% responders
  24% non- responders
- Κανένας ασθενής AEAs !!!
- Υψηλά επίπεδα etanercept σε όλους !!!

Vries,Wolbink ARD 2008

CONCISE REPORT

Patients non-responding to etanercept obtain lower etanercept concentrations compared with responding patients

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► Additional data (supplementary text and tables) are published online only. To view these files please visit the journal online (http://ard.bmj.com/content/71/1.toc).

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Accepted 12 August 2011
Published Online First 12 September 2011

ABSTRACT

Objective To investigate the relationship between serum etanercept levels and clinical response.

Methods In 292 etanercept-treated patients with rheumatoid arthritis clinical and pharmacological data were determined at baseline and after 1, 4 and 6 months of etanercept treatment. Differences in etanercept levels between good, moderate and European League Against Rheumatism (EULAR) non-responders were assessed after 6 months of therapy.

Results After 6 months of therapy etanercept levels were significantly higher in good responders (median (IQR) 3.78 (2.53–5.17)) compared with both moderate 3.10 (2.12–4.47) and EULAR non-responders 2.80 (1.27–3.93) (all $p<0.05$). There was a significant association between clinical response and serum etanercept levels (regression coefficient 0.54, 95% CI 0.21 to 0.86, $p=0.001$). When patients were categorised into quartiles according to the height of etanercept levels, the lowest quartile (etanercept level <2.1 mg/l) comprised 40% of all non-responders. The highest quartile (etanercept level >4.7 mg/l) comprised 35% of all good EULAR responders. Anti-etanercept antibodies were detected in none of the sera.

Conclusion The authors demonstrated that lower

found between etanercept drug levels and clinical response.[2 8] Furthermore, antibodies against etanercept, all non-neutralising, were measured in less than 2% of the patients.[8–10] In rheumatoid arthritis (RA) patients, a lower response to etanercept was associated with high levels of disability, the presence of IgM rheumatoid factor and etanercept monotherapy.[11 12]

Although a personalised treatment strategy has been proposed for patients treated with TNF inhibitors,[3 6] the clinical consequence of monitoring circulating etanercept levels is not yet clear. Therefore, we aimed to investigate the association between circulating etanercept levels and clinical response in a large cohort of etanercept-treated RA patients.

PATIENTS AND METHODS

Study population

The study population consisted of patients with RA, all treated with etanercept, included in an observational cohort. Inclusion criteria for this cohort were RA according to the American College of Rheumatology 1987 criteria,[13] age 18 years or older, failure on at least two disease-modifying antirheumatic drugs including methotrexate[14] and active

Etanercept σε ασθενείς με RA

- Nonresponders: Χαμηλότερα επίπεδα φαρμάκου
- Κανένας ασθενής AEAs !!

(Μακροπρόθεσμα ;)

Development of Antidrug Antibodies Against Adalimumab and Association With Disease Activity and Treatment Failure During Long-term Follow-up

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Michael T. Nurmohamed, MD, PhD
Pauline A. van Schouwenburg, MSc
Willem F. Lems, MD, PhD
Jos W. R. Twisk, PhD
Ben A. C. Dijkmans, MD, PhD
Lucien Aarden, PhD
Gerrit Jan Wolbink, MD, PhD

Context Short-term data on the immunogenicity of monoclonal antibodies showed associations between the development of antidrug antibodies and diminished serum drug levels, and a diminished treatment response. Little is known about the clinical relevance of antidrug antibodies against these drugs during long-term follow-up.

Objective To examine the course of antidrug antibody formation against fully human monoclonal antibody adalimumab and its clinical relevance during long-term (3-year) follow-up of patients with rheumatoid arthritis (RA).

Design, Setting, and Patients Prospective cohort study February 2004-September 2008; end of follow-up was September 2010. All 272 patients were diagnosed with RA and started treatment with adalimumab in an outpatient clinic.

Main Outcome Measures Disease activity was monitored and trough serum samples were obtained at baseline and 8 time points to 156 weeks. Serum adalimumab con-

for several therapeutics such as infliximab, adalimumab, and natalizumab.[1-7] Most studies were of 6 to 12 months' duration and showed that the presence of antidrug antibodies was associated with low to absent serum drug levels and a diminished treatment response, or even exacerbation of the underlying disease. These associations raise questions regarding the extent to which antidrug antibodies influence treatment response or, in other words, how clinically relevant the development of antidrug antibodies is. In addition, how the presence of antidrug antibodies should direct clinicians' management has been a subject of debate.[8] These questions can be applied to all diseases in which biologic therapeutics are used.

mumab antibodies more often discontinued participation due to treatment failure (n=29 [38%]; hazard ratio [HR], 3.0; 95% CI, 1.6-5.5; $P<.001$) compared with antiadalimumab antibody–negative ones (n=28 [14%]). Ninety-five of 196 patients (48%) without antiadalimumab antibodies had minimal disease activity vs 10 of 76 patients (13%) with antiadalimumab antibodies; patients with antiadalimumab antibodies less often had sustained minimal disease activity score in 28 joints (DAS28) (<3.2; HR, 3.6; 95% CI, 1.8-7.2; $P<.001$) compared with antiadalimumab antibody–negative ones. Three of 76 patients (4%) with antiadalimumab antibodies achieved sustained remission compared with 67 of 196 (34%) antiadalimumab antibody–negative ones; patients with antiadalimumab antibodies less often achieved remission (DAS28 <2.6; HR, 7.1; 95% CI, 2.1-23.4; $P<.001$) compared with antiadalimumab antibody–negative ones.

Conclusion Among outpatients with RA in whom adalimumab was started over 3 years, the development of antidrug antibodies was associated with lower adalimumab concentration and lower likelihood of minimal disease activity or clinical remission.

JAMA. 2011;305(14):1460-1468 www.jama.com

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- Διαρκεια μελέτης 3 έτη
- 272 ασθενείς
- 76 ασθ (28%) AAAs(+)
- 51 απ’αυτούς στις 28 πρώτες εβδ

- 48% ασθ με AAAs(-)…DAS28<3.2
- 13% ασθ με AAAs(+) …DAS28<3.2
- 34% ασθ με AAAs(-)…DAS28<2.6
- 4% ασθ με AAAs(+)…DAS28<2.6

Ασθενείς με AAAs(+)

- Ή δεν ελάμβαναν MTX !!
- Ή ελάμβαναν μικρότερες δόσεις !

ARD Online First, published on May 14, 2012 as 10.1136/annrheumdis-2012-201544

Methotrexate reduces immunogenicity in adalimumab treated rheumatoid arthritis patients in a dose dependent manner

Immunogenicity of adalimumab could impair important treatment outcome parameters in patients with rheumatoid arthritis (RA). Patients who developed antiadalimumab antibodies (AAA) during a 3 year time period achieved less often minimal disease activity or remission and treatment failure occurred more often compared with patients without AAA.[1] There were remarkable baseline differences: patients developing AAA had more long-standing, severe disease and less often used concomitant medication including lower doses of methotrexate (MTX), compared with patients not developing AAA. In literature, a favourable effect of concomitant MTX use on the immunogenicity of adalimumab for several inflammatory conditions is suggested.[2] discontinued.[3] Additionally, in ankylosing spondylitis patients with axial symptoms there is no proof for efficacy of MTX.[4]

In a murine Pompe disease model, low dose administration of MTX (0.5 mg/kg) within 24 h after enzyme replacement treatment induced a significant reduction in antidrug antibody formation.[5] In this model, 0.5 mg/kg, administered three times, represented a human dose of 0.6 mg/week for a 5 kg infant, which is lower than the MTX dose prescribed for the treatment of adult RA.[5] Furthermore, this model showed that MTX should be initiated at the start of the immunogenic therapy because with MTX therapy it was not possible to abolish ongoing antidrug antibody formation.[5 6] In a human study with infliximab treated RA patients, 7.5 mg MTX weekly was sufficient in reducing immunogenicity of infliximab; however, in that study there was no comparison with other MTX doses.[7]

The mechanism whereby MTX acts on the immune response remained unsolved; however, we hypothesise that suppression of early T and B cell expansion might be responsible for the modulation of the immune response. Others hypothesise that there is an additional or synergistic effect because MTX reduces inflammation whereby drug levels and response rates are increased.[8]

the optimisation of treatment responses and easy applicable in clinical practice.

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Accepted 14 April 2012

a research grant from Pfizer (Wyeth) (paid to the Institution) and payments for lectures from Pfizer and Amgen.

Ethics approval The study was approved by the medical ethics committee of Reade and Slotervaart Ziekenhuis.

Provenance and peer review Not commissioned; externally peer reviewed.

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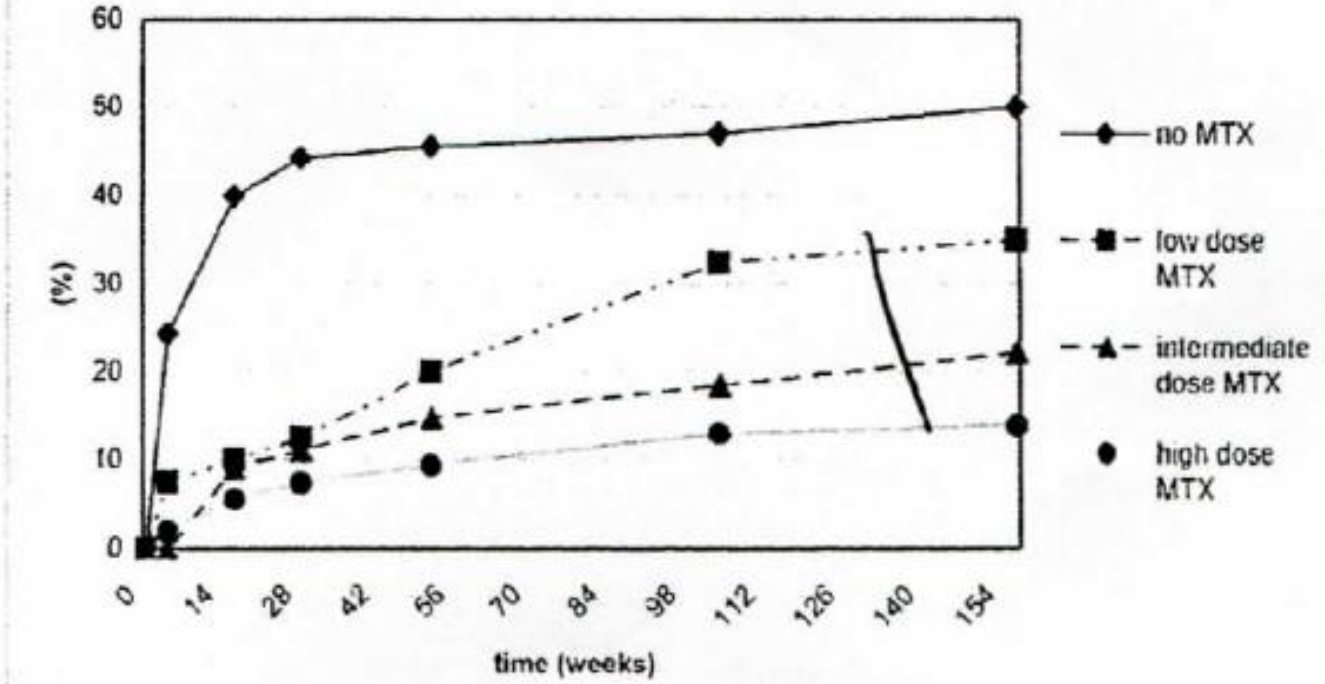


Figure 1 Percentage of patients developing antiadalimumab antibodies (AAA) per baseline methotrexate (MTX) dose group. No MTX (0 mg/week, n=70), low dose MTX (5–10 mg/week, n=40), intermediate dose MTX (12.5–20 mg/week, n=54), or high dose MTX (≥22.5 mg/week, n=108).

Ασθενείς με AAAs(+) είχαν επίσης…

- Γενετικές διαφορές

  (πολυμορφισμός IL-10)

- Διαφορές baseline χαρακτηριστικών

  - υψηλότερο DAS28
  - υψηλότερη CRP
  - μεγαλύτερη διάρκεια νόσου
  - περισσότερες διαβρώσεις

Figure 1. Percentage of Antiadalimumab Development Over Time

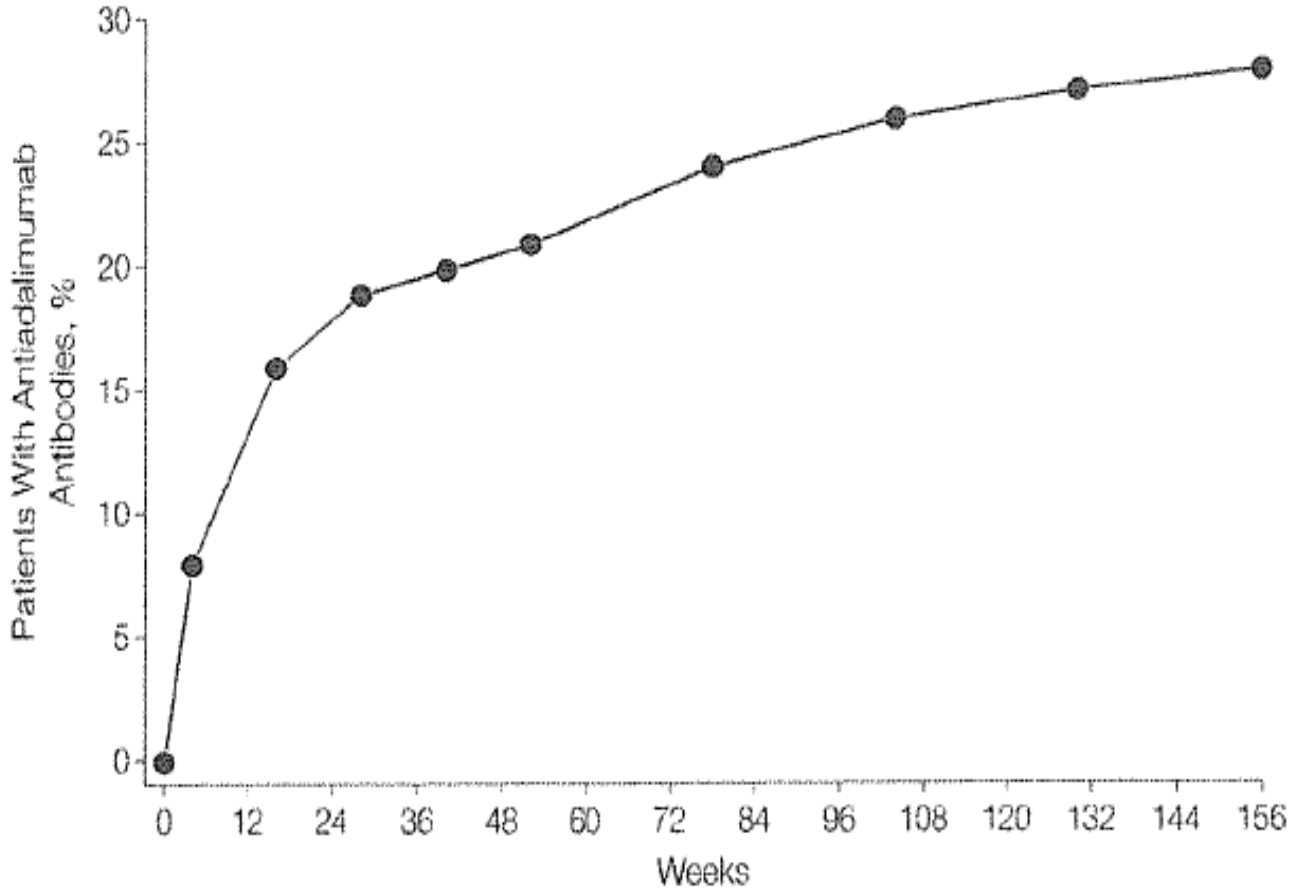


Figure 2. Median Adalimumab Concentrations Over Time

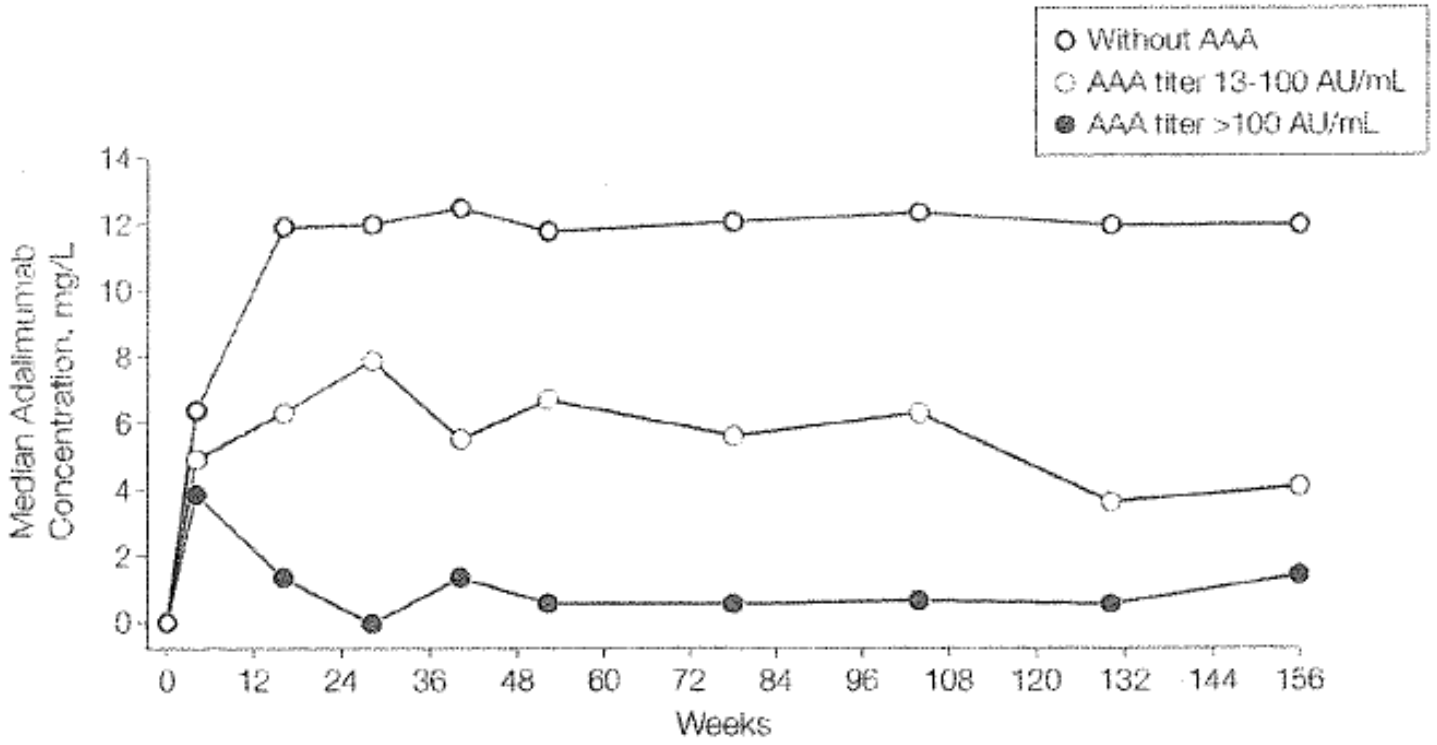


Figure 4. Overall Patient Dropout and Dropout Due to Treatment Failure

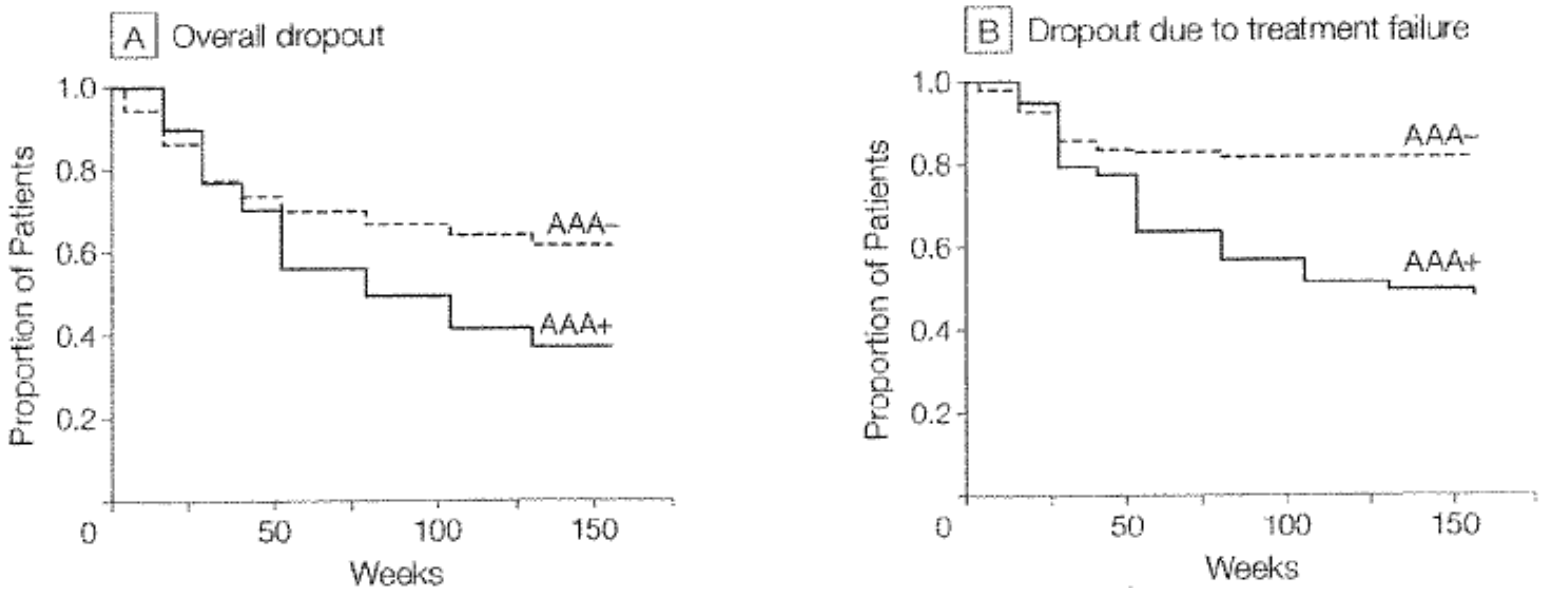
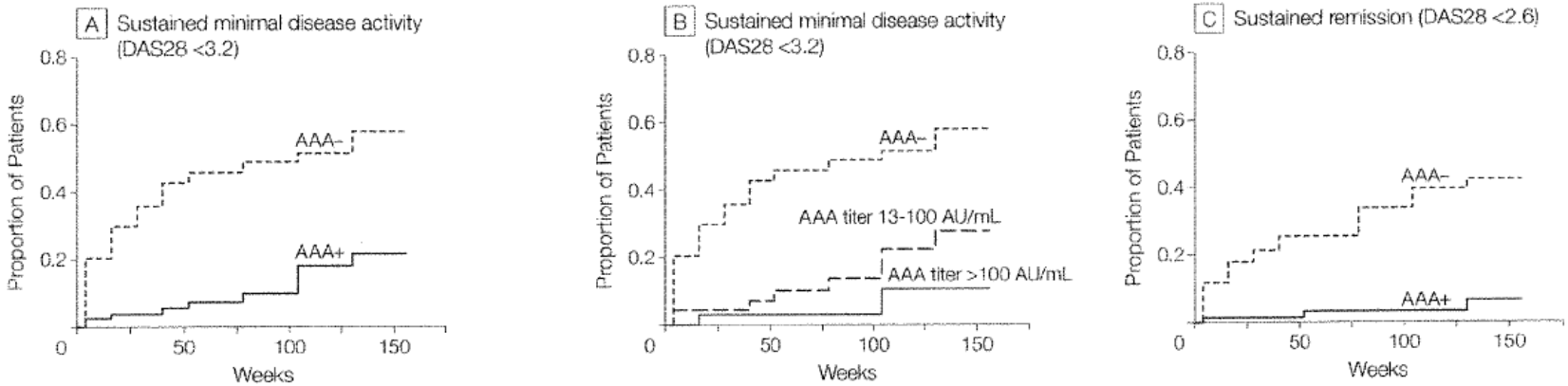


Figure 5. Sustained Disease Activity and Remission in Patients With and Without Antiadalimumab Antibodies



Switching και….

- Παρουσία αντισωμάτων
- Επίπεδα φαρμάκου

Bartelds ARD 2010

Jamnitski ARD 2011

Immunogenicity-κλινική σημασία

- Ab πιθανότατα σε κάθε Βιολογικό

- Επηρεάζουν την δημιουργία τους:

  - η δόση
  - τα συγχορηγούμενα φάρμακα(MTX)
  -η δομή του Βιολογικού
  -γενετικοί παράγοντες(HLA)

Επομένως…(1)

- Σημαντική η συγχορήγηση MTX
- Ίσως υψηλότερες δόσεις Βιολογικού
- (Ίσως συγχορήγηση MTX και σε AS,PsA)

Επομένως…(2)

- Ανάγκη για “drug monitoring”
- ΟΧΙ χορήγηση Βιολογικών βασισμένη στο “one size fits all”
- Αποφάσεις για αλλαγή τους(και επιλογή αντικαταστάτη) όχι μόνο “κλινικώς”

Εναρξη anti-TNFσε ασθενείς με RA

- Συχνά…Primary Nonresponders
- Συνήθως…αύξηση δόσης ή αύξηση συχνότητας χορήγησης
- Πολλοί και πάλι….Non responders

- Πολλοί απ’ αυτούς…Υψηλά επίπεδα anti-TNF !!!!!

- Άλλοι Χαμηλά επίπεδα φαρμάκου και Υψηλά επίπεδα αντισωμάτων !!!

Επιμένοντας…

- απώλεια χρόνου
- χρήματος
- risk

Επομένως…(3)

Εξατομικευμένη θεραπεία βασισμένη σε:

- μετρήσεις ΕΝΕΡΓΟΤΗΤΑΣ νόσου (π.χ DAS28)
- αλλά και **μετρήσεις επιπέδων ΦΑΡΜΑΚΟΥ**
- και **μετρήσεις επιπέδων ΑΝΤΙΣΩΜΑΤΩΝ**

Ίσως…όταν Ab(-)

- Σε ασθενείς **(responders)** με υψηλά επίπεδα φαρμάκου …αύξηση των μεσοδιαστημάτων χορήγησης

- Σε ασθενείς **(nonresponders)** με χαμηλά επίπεδα φαρμάκου…αύξηση της δόσης του

Ίσως…σε non-responders με Ab(+) καί χαμηλά επίπεδα φαρμάκου

- Αλλαγή σε παρόμοιου τύπου θεραπεία αλλά διαφορετικής πρωτεϊνικής δομής (π.χ από infliximab σε etanercept ή adalimumab)

Ίσως…σε non-responders με υψηλά επίπεδα φαρμάκου

- Switching σε Βιολογικό παράγοντα πού δρά σε διαφορετικό «μονοπάτι» (pathway)

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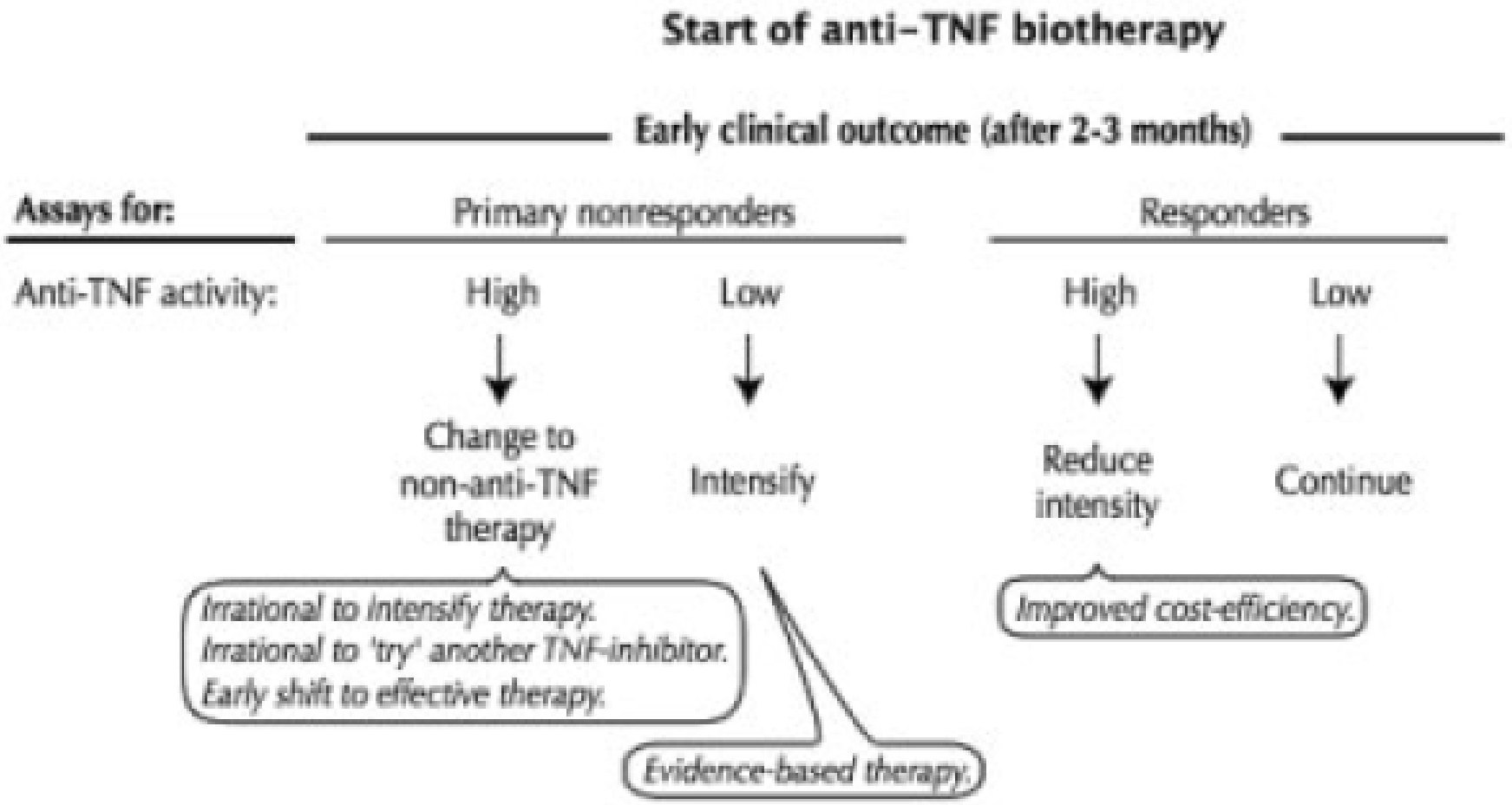
EDITORIAL

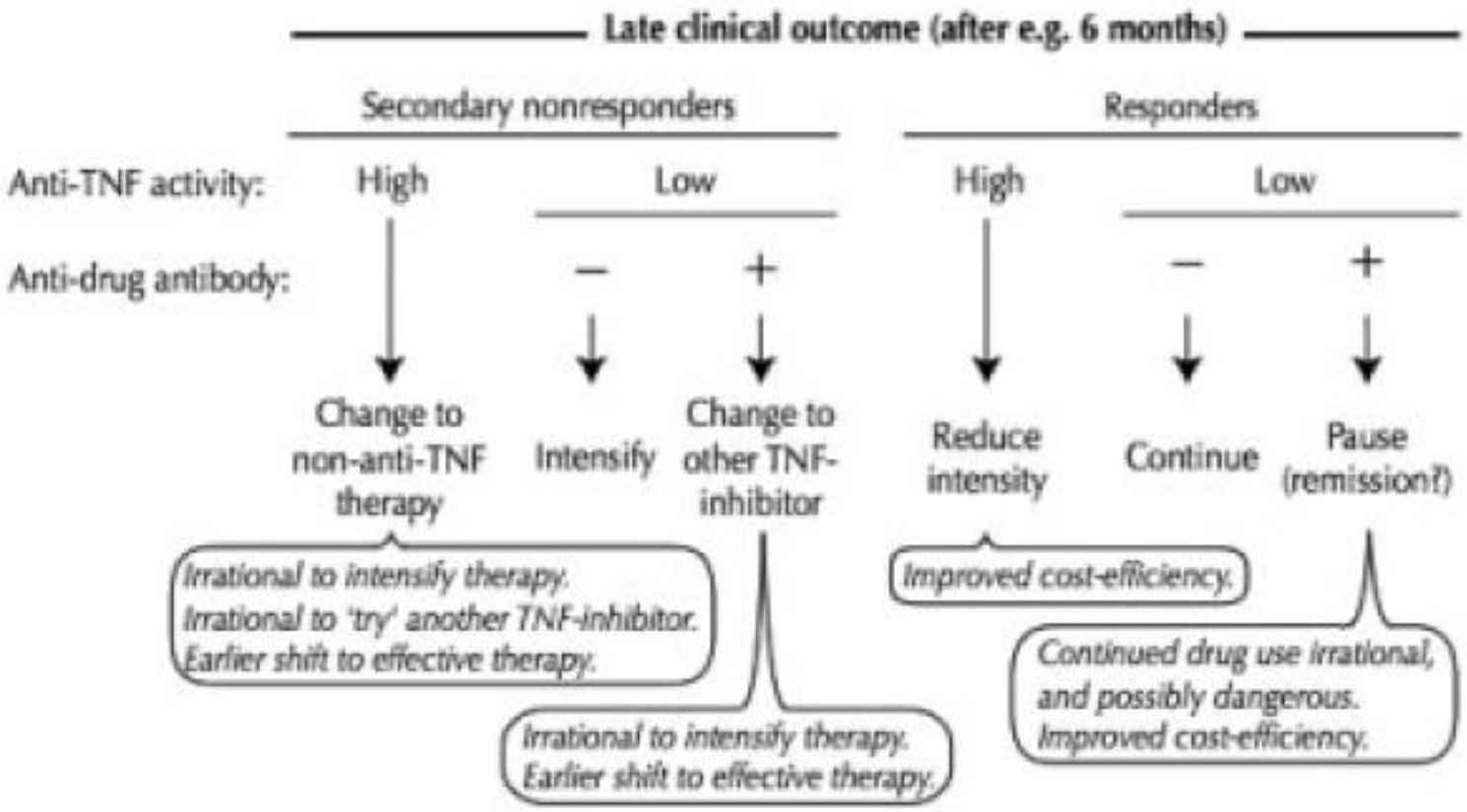
Is There a Need for Immunopharmacologic Guidance of Anti–Tumor Necrosis Factor Therapies?

Klaus Bendtzen

The last decade has seen a revolution in the treatment of patients with inflammatory rheumatic dis-

injections of nonself protein
with clinically overt side effe


Start of anti-TNF biotherapy
Early clinical outcome (after 2-3 months)
Assays for:
Primary nonresponders
Responders
Anti-TNF activity:
High
Low
High
Low
Change to non-anti-TNF therapy
Intensify
Reduce intensity
Continue
Irrational to intensify therapy.
Irrational to 'try' another TNF-inhibitor.
Early shift to effective therapy.
Evidence-based therapy.
Improved cost-efficiency.

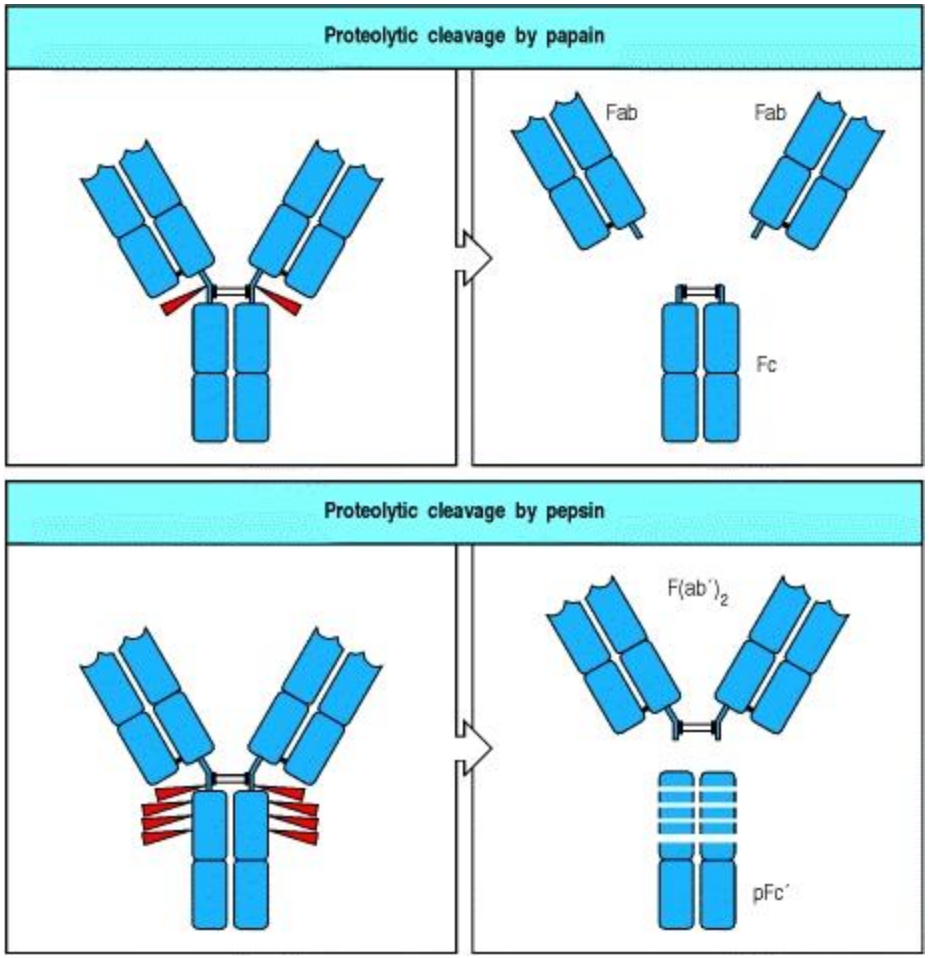

Late clinical outcome (after e.g. 6 months)
Secondary nonresponders
Responders
Anti-TNF activity:
High
Low
High
Low
Anti-drug antibody:
–
+
–
+
Change to non-anti-TNF therapy
Intensify
Change to other TNF-inhibitor
Reduce intensity
Continue
Pause (remission?)
Irrational to intensify therapy.
Irrational to 'try' another TNF-inhibitor.
Earlier shift to effective therapy.
Irrational to intensify therapy.
Earlier shift to effective therapy.
Improved cost-efficiency.
Continued drug use irrational, and possibly dangerous.
Improved cost-efficiency.

- Ανοσογονικότητα Βιολογικών…δεδομένη
- Standardization μεθόδου μέτρησης
- Consensus για timing μέτρησης
- Monitoring επιπέδων φαρμάκου (TmAb) και αντισώματος (anti-TmAb)
- Συγχορήγηση κατάλληλης δόσης MTX

This is

THE END

Immunoglobulin Structure: Fc and Fab regions are functionally distinct



Immunobiology: The Immune System in Health and Disease. 5th edition

Fab: fragment, Ag binding

Fc: fragment crystallizable

Rodney R. Porter
(1917-1985)
Nobel Prize in Medicine 1972