Biyolojik İmmünojenitesi

Doç.Dr.Savaş Yaylı
Karadeniz Teknik Üniversitesi Tıp Fakültesi
Deri ve Zührevi Hastalıklar AD, Trabzon

III.Dermatoonkoloji Günleri, Bakü, 05.09.2014

İmmünojenite: Sunu planı & Sorular

- Tanımlar
- Etkili faktörler neler?
- Moleküler yapı ne kadar etkili?
- Hasta yönetimine etkisi var mı?
- Kontrol mümkün mü?
- Tedavi optimizasyonu nasıl yapılmalı?
- Mesajlar

İmmünojenite / Tanımlar

Protein bir ilacın immün yanıt oluşturma yeteneği

Adaptif immün sistemin up-regülasyonu

- Eksojen maddenin yabancı olarak tanınması
- İmmün yanıt oluşturma
  - Direkt nötralizasyon
  - Kompleman aktivasyonu
  - Eliminasyonu hızlandıran işaretleme
- Anti-drug antikorların üretimi (ADA)

ADA /biyolojik ajan kompleksi oluşturma

- Klirens artışı ile serum ilaç düzeyinde azalma
- Biyolojiklerin direkt nötralizasyonu

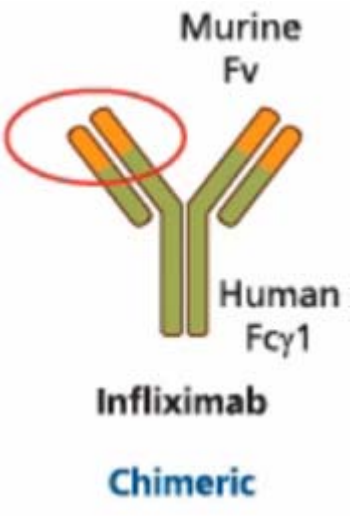
Jani M, et al. Rheumatology 2014. *Carrascosa JM. Actas Dermosifiliogr 2013*

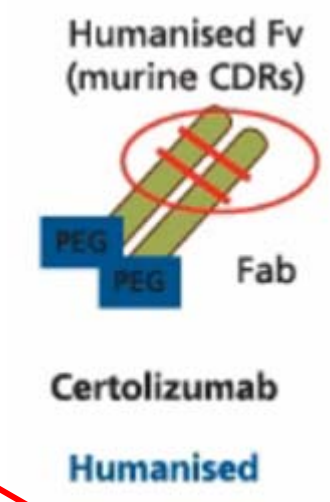
İmmünojenite: Ne etkili?

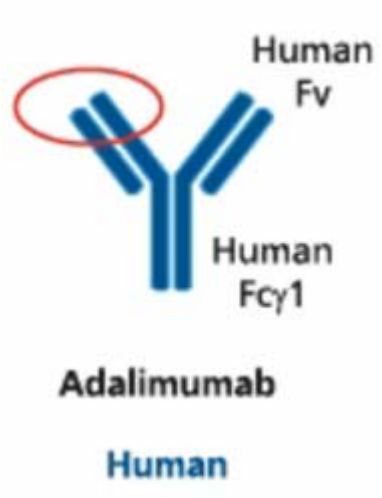
- Moleküler yapı
- Tedavi şeması
  - Toplam süre, doz
  - Aralıklı > kesintisiz
  - Uygulama yolu (im, sc > iv)
- Hasta özellikleri
  - Genetik
  - Yaş
  - Hastalığın tipi: kanser & inflamatuar
  - Önceki ilaç maruziyetleri
- Eşzamanlı immünsupresyon (RA,PSO?)
  - MTX?

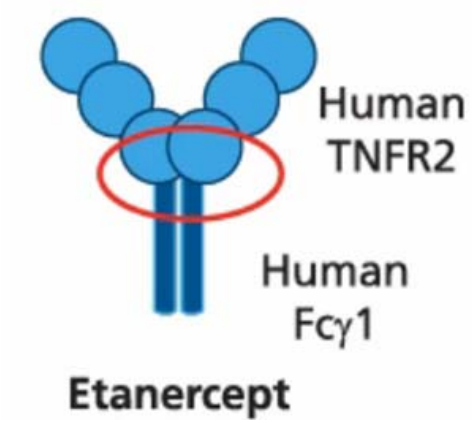
Carrascosa JM, et al.JEADV 2014 *Jani M, et al. Rheumatology 2014*

Moleküler yapı & İmmünojenite





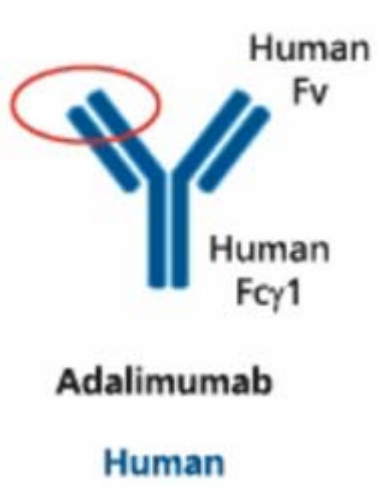




İmmünojenitede azalma

Jani M, et al. Rheumatology 2014

Moleküler yapı & İmmünojenite

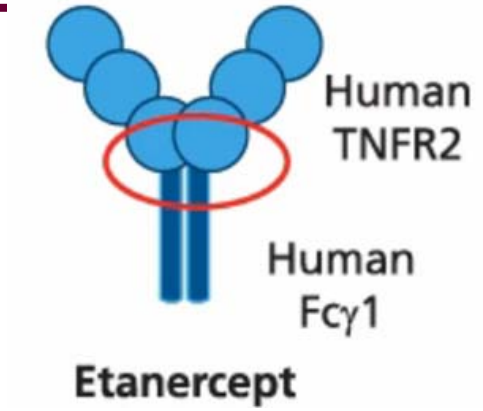


Tamamen insan mAb da immünojenik reaksiyon oluşturabilir

✓ Fab değişken bölgesinde çok sayıda epitop

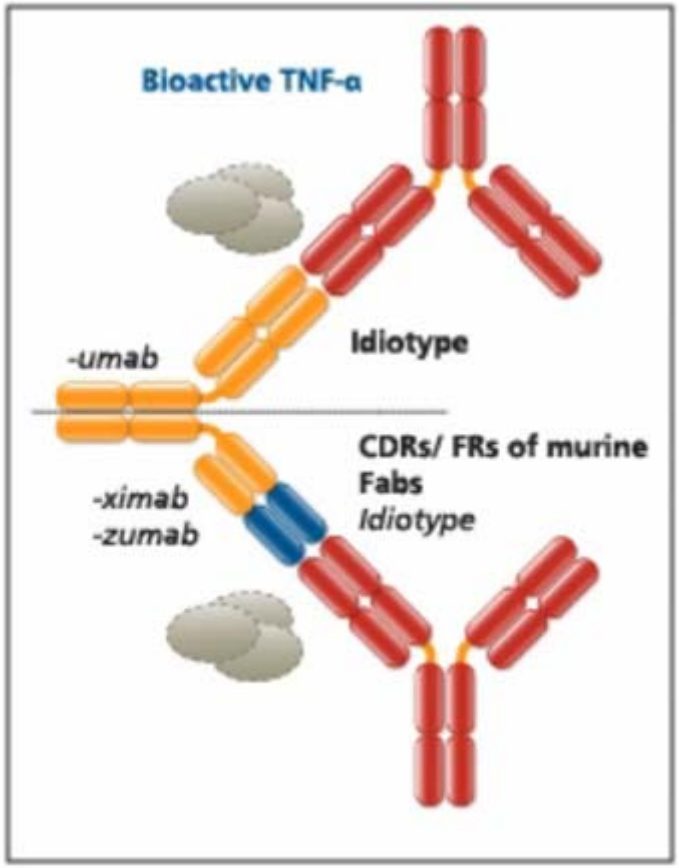
Etanersept-ADA terapötik etkiyi değiştirmez

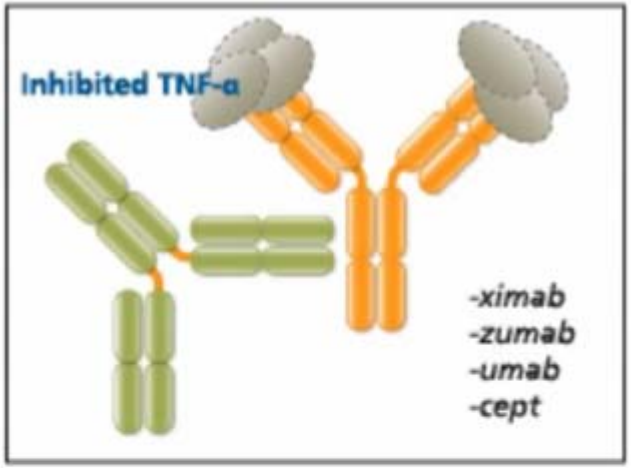
✓ ADA(ETA): TNF reseptörleri/IgG1 Fc kısmı bağlantısına

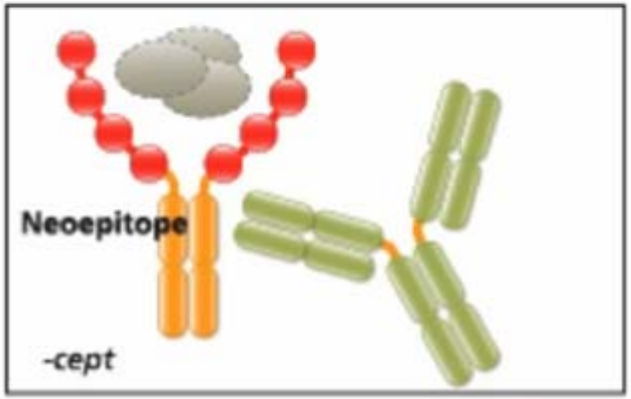


Vincent FB, et al. Ann Rheum Dis 2013
Carrascosa JM. Actas Dermosifiliogr 2013

ADA







Nötralizan ADA

Proteinin aktif kısmına bağlanır

- Aktiviteyi direkt olarak etkiler
- Klirensi arttırır

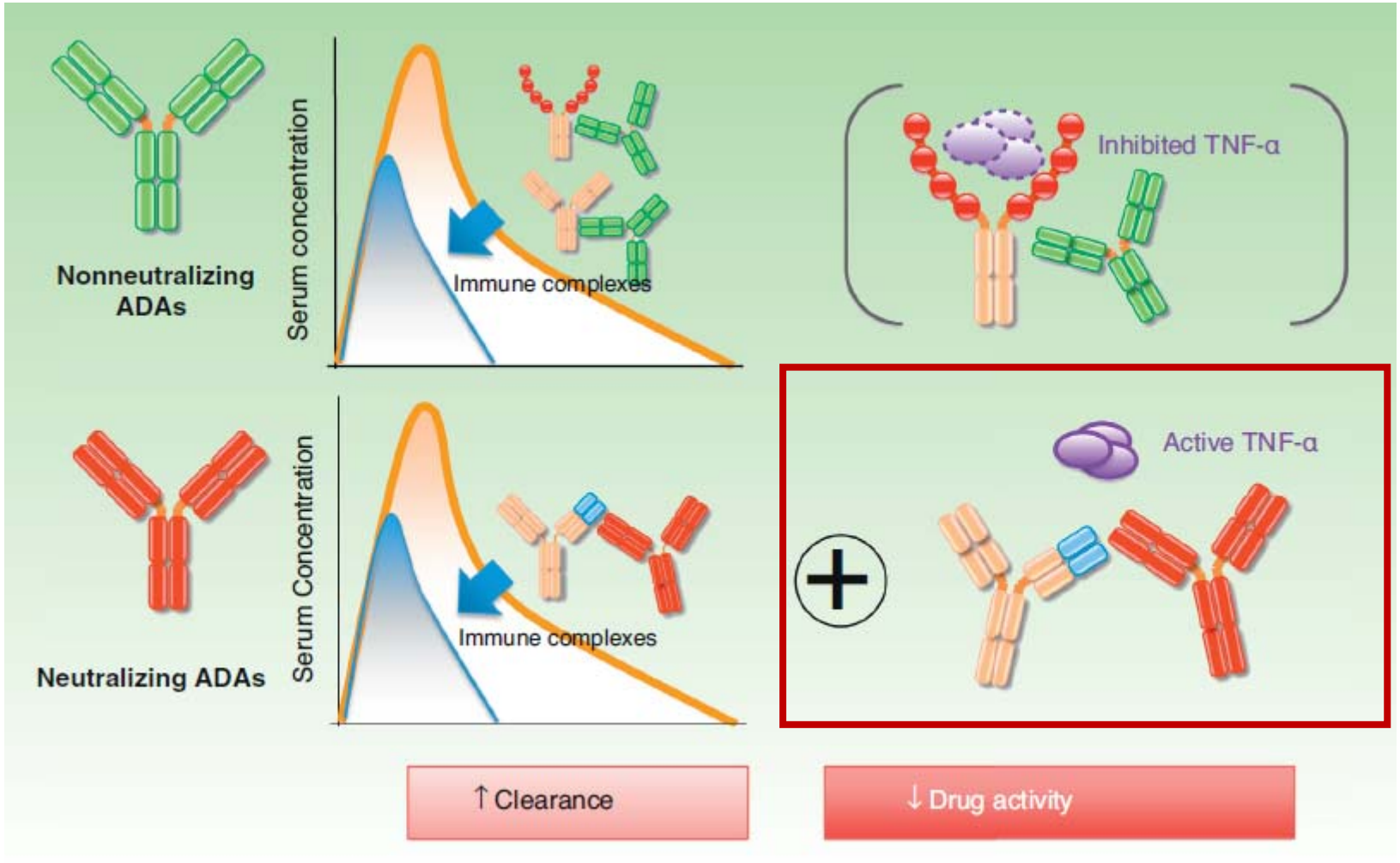
Non-Nötralizan ADA

Proteinin terapötik etki ile ilişkisiz bir kısmına bağlanır

- Klirensi arttırır

Carrascosa JM. Actas Dermosifiliogr 2013

ADA



Carrascosa JM. Actas Dermosifiliogr 2013

İmmünojenite & Hasta yönetiminde izler

JDDG Journal of the German Society of Dermatology
DOI: 10.1111/j.1610-0379.2012.07919.x

Guidelines on the Treatment of Psoriasis Vulgaris

Actas Dermosifiliogr. 2013;104(8):694–709

Guideline

S3 – G
(Engl

ACTAS
Dermo-Sifiliográficas
Full English text available at
www.actasdermo.org

CONSENSUS DOCUMENT

Spanish Evidence-Based Guidelines on the Treatment of Psoriasis With Biologic Agents, 2013. Part 1: On Efficacy and Choice of Treatment☆

- Biyolojiklerin etkinliğinde azalma!!
- Yan etkilerin gelişmesi!!

  İnfüzyon reaksiyonları (İnfliksimab)

The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases:

12 çalışma
865 hasta
540 RA
132 spA
58 PSO

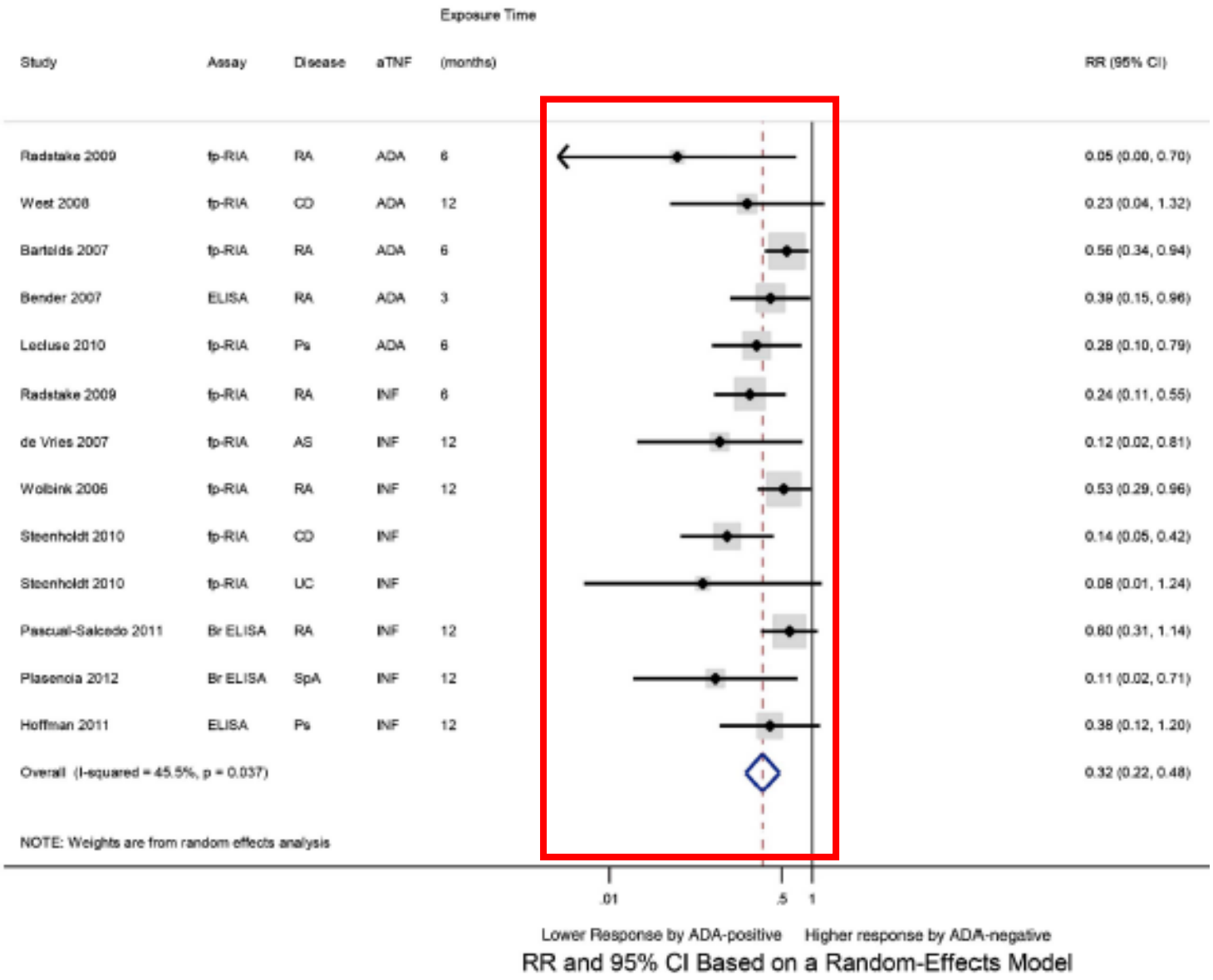


Table 1. Anti-drug antibodies and their association with serum drug trough levels and clinical efficacy.

Study (year)	Biologic	ADA prevalence	ADA positivity	Ref.
			Relation to drug trough levels and clinical efficacy	
Leonardi *et al.* (2003)	ETA	8 patients	No significant difference in clinical efficacy	[9]
Papp *et al.* (2005)	ETA	2.7% (15/549)	No significant difference in clinical efficacy	[29]
Gordon *et al.* (2006)	ETA	4.7% (14/297)	No significant difference in clinical efficacy	[10]
Tyring *et al.* (2007)	ETA	18.3% (111/606)	No significant difference in clinical efficacy	[30]
Leonardi *et al.* (2010)	ETA	15.2% (130/857)	No significant difference in clinical efficacy	[28]
Mahil *et al.* (2013)	ETA	0% (0/25)	Unable to assess	[31]
Gottlieb *et al.* (2004)	INF	23.3% (38/163)	Not reported	[35]
Reich *et al.* (2005)	INF	26.5% (70/264)	Decreased PASI 75 response	[11]
Krathen *et al.* (2006)	INF	16.4% (12/73)	Decreased clinical efficacy in 1 year	[38]
Menter *et al.* (2007)	INF	43.6% (237/543)	Decreased maintenance of clinical response	[27]
Adisen *et al.* (2010)	INF	33.3% (5/15)	Decreased PASI response	[34]
Torii & Nakagawa (2010)	INF	20% (10/50)	Decreased drug trough levels and PASI 75 response	[41]
Hoffmann *et al.* (2011)	INF	20.7% (6/29)	Decreased clinical response	[37]
Torii *et al.* (2011)	INF	29.7% (19/64)	Not reported	[40]
Gottlieb *et al.* (2012)	INF	5.4% (9/168)	Undetectable drug trough levels	[36]
Takahashi *et al.* (2013)	INF	30% (6/20)	Decreased drug trough levels and clinical response	[39]
Menter *et al.* (2008)	ADL	8.8% (73/825)	Reduced efficacy	[25]
Leduse *et al.* (2010)	ADL	44.8% (13/29)	Decreased drug trough levels and clinical response	[26]
Asahina *et al.* (2010)	ADL	10.6% (13/123)	Decreased PASI response	[55]
Takahashi *et al.* (2013)	ADL	15.6% (5/32)	Decreased drug trough levels and clinical response	[39]
Mahil *et al.* (2013)	ADL	6.4% (2/31)	Preponderance in non-responders	[31]
Kauffman *et al.* (2004)	UST	5.5% (1/18)	Not reported	[65]
Krueger *et al.* (2007)	UST	4.1% (12/293)	Not reported	[64]
Papp *et al.* (2008)	UST	5.4% (65/1202)	Preponderance for decreased drug trough levels and clinical response	[62]
Griffiths *et al.* (2010)	UST	3.9% (32/835)	Not reported	[61]
Tsai *et al.* (2011)	UST	4.4% (5/112)	Preponderance for decreased PASI 75 response	[63]
Kimball *et al.* (2012)	UST	5.2% (39/746)	No significant difference in clinical response	[24]

Hsu L, et al. Expert Rev Clin İmmunol 2013

DOI: 10.1111/jdv.12549 JEADV

REVIEW ARTICLE

Clinical relevance of immunogenicity of biologics in psoriasis: Implications for treatment strategies

J.-M. Carrascosa,[1,*] M.B.A. van Doorn,[2] M. Lahfa,[3] F.O. Nestle,[4] D. Jullien,[5,6] J.C. Prinz[7]

14 klinik çalışmanın entegre analizi

Biological drug	Molecule	No of studies	No of patients	ADA (%)	Association of ADA with:	
					Clinical response	Adverse events
Adalimumab[30–34]	Humanized MAb	4	1194	6–46	Yes	No
Brodalumab[42]	Humanized MAb	1	160	5.0–9.8	–	–
Certolizumab pegol[41]	PEGylated Fab fragment of humanized MAb	1	188	4–25	No	–
Etanercept[15,35–37]	Fusion protein	4	2138	1.1–18.3	No	No
Golimumab[45]	Humanized MAb	1	405	5.4	–	
Infliximab[26–29,34]	Chimeric MAb	5	675	19.5–51.5	Yes	Yes
Secukinumab[43,44]	Fully human MAb	2	413	0	–	–
Ustekinumab[38–40]	Fully human MAb	3	2328	3.8–5.1	Yes	No

JAMA Dermatol. 2014 Feb;150(2):130-6. doi: 10.1001/jamadermatol.2013.8347.

Extent and consequences of antibody formation against adalimumab in patients with psoriasis: one-year follow-up.

Menting SP[1], van Lümig PP[2], de Vries AC[1], van den Reek JM[2], van der Kleij D[3], de Jong EM[2], Spuls PI[1], Lecluse LL[1].

Author information

Abstract

IMPORTANCE: In a previously reported cohort of 29 patients with plaque-type psoriasis followed up for 24 weeks, clinically relevant antidrug antibody (ADA) to adalimumab was frequently found. Long-term data were lacking. We now present the extension of this study: 80 patients followed up for 1 year.

OBJECTIVES: To assess the extent of ADA and its clinical consequences after 24 weeks of adalimumab treatment for psoriasis in a cohort of 80 patients.

DESIGN, SETTING, AND PARTICIPANTS: A multicenter cohort study, performed in the outpatient dermatology clinic of 2 academic hospitals, included 80 sequential patients receiving adalimumab therapy for plaque-type psoriasis and had a follow-up of 1 year. Outcome assessors were not aware of the presence of antibodies to adalimumab or the adalimumab serum concentration when assessing patients' Psoriasis Area and Severity Index (PASI), and personnel analyzing serum samples were blinded to patients' PASI.

INTERVENTIONS: For 80 patients treated with adalimumab for psoriasis, disease severity (PASI) was assessed, blood samples were collected, and adalimumab and ADA concentrations was determined at baseline and at weeks 12, 24, and 52.

MAIN OUTCOMES AND MEASURES: Patient PASI and adalimumab and ADA concentrations.

RESULTS: Antidrug antibody formed in 49% of patients, before week 24 in 90% of them. Adalimumab and ADA concentrations, clinical response and ADA concentration, and adalimumab concentration and clinical response had correlations of -0.872, -0.606, and 0.519, respectively. The adalimumab dose interval was shortened because of lack of efficacy in 15 patients, 7 with and 8 without ADA; improvement in responder status occurred in 1 of 7 and 4 of 8, respectively.

CONCLUSIONS AND RELEVANCE: Patients with no ADA formation in the first 24 weeks of treatment have little chance of it in the following 24 weeks. The presence of ADA is strongly correlated with adalimumab concentration and greatly influences clinical response. If ADA is present, dose interval shortening is less useful.

İmmünojenite & Tedaviye etki: "Drug survival"?

J Drugs Dermatol. 2009 Apr;8(4):329-33.

Biologic survival.

Noiles K[1], Vender R.

Author information

Abstract

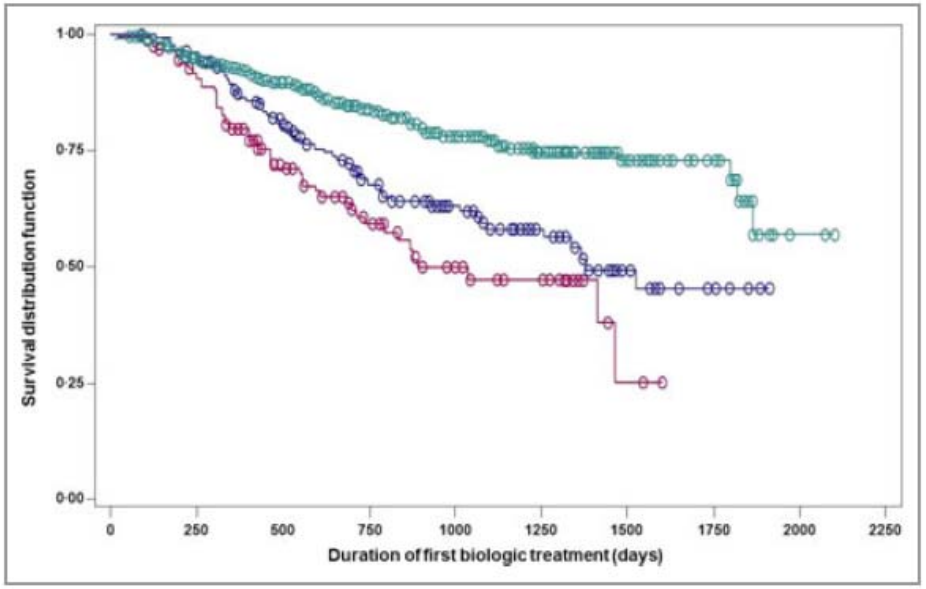
BACKGROUND: The results of long-term studies on the efficacy and safety profiles of the biologics for patients with psoriasis are starting to appear in the literature. Not only are the results promising for the biologics as a whole, but the high number of patients remaining in these clinical trials after extended periods of time, or retention, may also reflect additional benefits of these biologics. The aim of this review was to manuscript aims to compare rates of attrition for the various biologic therapies in pivotal clinical trials in order to assess and compare adherence of patients to long-term use of the different biologic agents, also known as biologic survival.

METHODS: An in-depth literature review was conducted using PubMed and MEDLINE. Randomized, controlled trials utilizing biologic agents as monotherapy for the treatment of psoriasis were analyzed for patient numbers over time. Studies which provided data on patient retention for at least 24 weeks were selected, graphed, and compared. Reasons for discontinuation were noted.

RESULTS: Nineteen trials were selected, graphed and charted to compare attrition rates of the various biologic therapies. Due to differences in sample size, study design, dosing regimens, study duration and limited data with regards to patient numbers, it is difficult to reach a definitive conclusion as to which biologic agent is associated with the lowest rate of discontinuation. However, given the data available, etanercept appears to be the most successful therapy in terms of patient retention in studies both greater than and less than 30 weeks. For the studies using various dosing regimens, intrastudy attrition rates are also compared.

CONCLUSION: While the data available thus far on patient retention for the biologic therapies are very limited, preliminary conclusions can be drawn. Among the available biologic agents, etanercept appears to be associated with the lowest rate of discontinuation. This may be due to greater superior effiacy and to a decreased likelihood of experiencing adverse events.

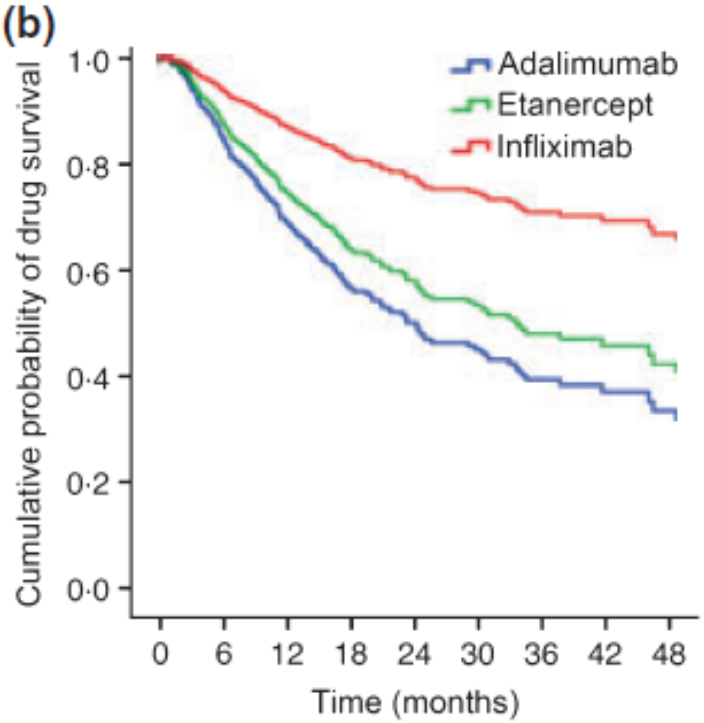
İmmünojenite & Tedaviye etki: "Drug survival"?



ETA

INF

ADAL



- Etki kaybı, "ilaçta kalım süre"sinin en önemli faktörlerinden!
- İnfliksimab: 1/3 hastada doz modifikasyonu!

Esposito M, et al. BJD 2013
Gniadecki R, et al. BJD 2011

İmmünojenite & Tedaviye etki: "Drug survival"?

- OSCAR study; 650 plak psoriasis hastası
- > 3 ay, ilk anti-TNF tedavisinde ilaçta kalım!

n (%)	İnfliksimab	Adalimumab	Etanersept	Toplam
Tedavide kalanlar	91 (61.9)	67 (58.8)	314 (80.7)	472 (72.6)
İlacı kesenler	56 (38.1)	47 (41.2)	75 (19.3)	178 (27.4)
İlaç kesimi nedeni				
Primer etkisizlik	9 (6.1)	9 (7.9)	16 (4.1)	34 (5.2)
Sekonder etkisizlik	32 (21.8)	22 (19.3)	40 (10.3)	94 (14.5)
Yan etkiler	13 (8.8)	5 (4.4)	11 (2.8)	29 (4.5)
Diğer nedenler	2 (1.4)	11 (9.6)	8 (2.1)	21 (3.2)

Esposito M, et al. BJD 2013

ADA & Yan etkiler

- İnfüzyon reaksiyonları (İNF)
- Enjeksiyon yeri reaksiyonları (ADAL / ETA/UST)
- İmmün kompleks vasküliti
- Serum hastalığı
- Anaflaksi

Bendtzen K, et al. Arthritis Rheum 2006
Vincent FB, et al. Ann Rheum Dis 2013

Psoriasisi yönetirken ADA: Ne zaman?

- Yanıt yokluğu / kaybı yaşayan hastalar (Primer / Sekonder)
  - Klinik: Muayene, PAŞİ
  - Yanıt kaybının nedenini: ADA?
- Yan etkiler yaşayan hastalar
  - Serum hastalığı
  - Vaskülit
- Tedaviye ara vermiş hastalarda yeniden tedavi başlarken
  - Aynı ilaç?
  - Aynı gruptan farklı mekanizma ile etkiyen ilaç?
  - Farklı bir gruptan ilaç?

Rivera R, et al. Actas Dermosifiliogr 2014

ADA testleri: Standart değil ☹

- Farklı yöntemler var
  - Spesifite ve sensitivite farklı
  - Değişken sonuçlar
- Psoriasislilerde geçerli değerler yok
  - ADA cut-offs?
  - Optimum ilaç seviyeleri?
- Çoğu testte önemli eksiklik ☹
  - Nötralizan / non-nötralizan ADA ayrımı?
- İmmünojenitede zamanla değişim
  - Tekrarlayan ölçümler gerekli

Rivera R, et al. Actas Dermosifiliogr 2014

ADA testleri: Karşılaştırma

ELISA	RIA	HMSA
Yüksek spesifite	Spesifite?	Yüksek spesifite Yüksek sensitivite
IgG4 tanımaz	IgG4 tanır	Tüm alt tipleri tanır (IgG4 dahil)
İlaç varlığında etkileşim	İlaç etkileşimi düşük	İlaç varlığında ölçüm +
Klinik çalışmalarda	Radyoaktif materyal	

- \+ İlaç düzeyleri ölçümü

  Sadece ADA testlerinden çok daha üstün

  ADA varlığı?

  Yanıt değerlendirmesinde belirteç

Hsu L, et al. Expert Rev Clin Immunol 2013
Wang SL, et al. J Immunol Methods 2012
Wang SL, et al. J Pharm Biomed Anal 2013

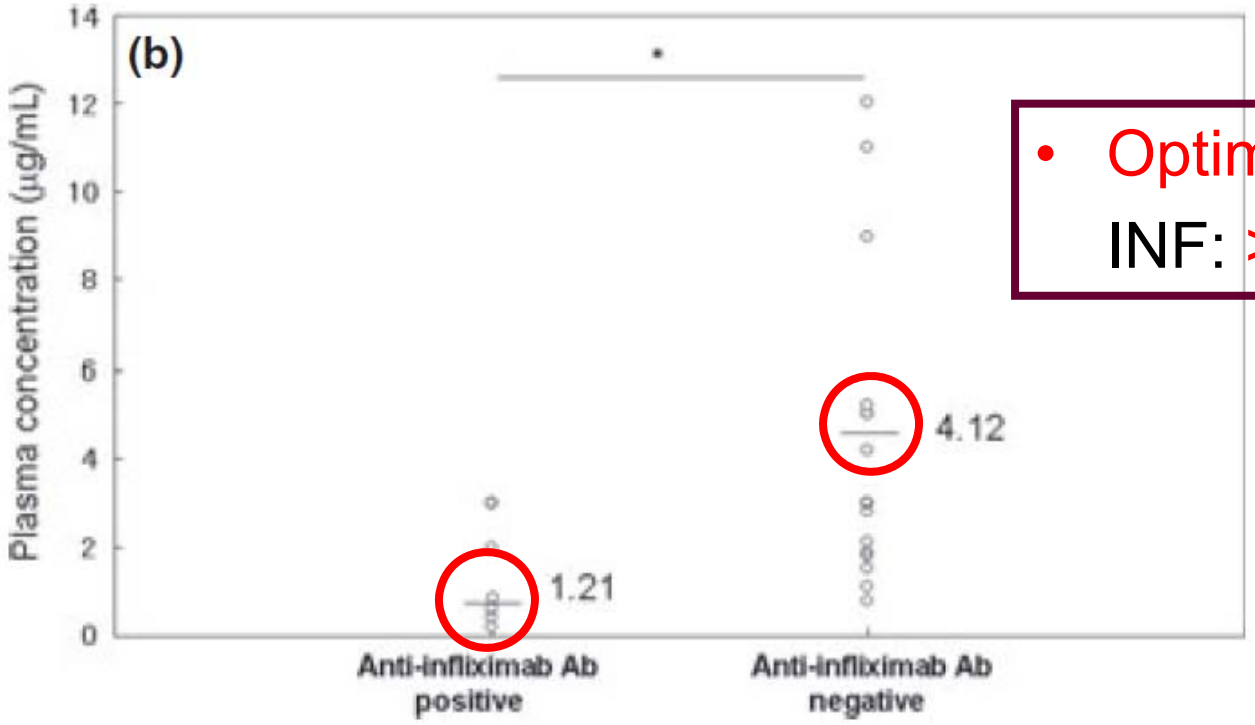
doi: 10.1111/j.1346-8138.2012.01679.x *Journal of Dermatology* 2013; **40**: 39–42

ORIGINAL ARTICLE

Plasma trough levels of adalimumab and infliximab in terms of clinical efficacy during the treatment of psoriasis

Hidetoshi TAKAHASHI, Hitomi TSUJI, Akemi ISHIDA-YAMAMOTO, Hajime IIZUKA

- INF ile tedavide 20 psoriasisli, 48.hafta
- İlaç düzeyleri ve ADA / PASI ile ilişki



- Optimal cut-off
  INF: >0.92 (>PASI75)

doi: 10.1111/j.1346-8138.2012.01679.x *Journal of Dermatology* 2013; **40**: 39–42

ORIGINAL ARTICLE

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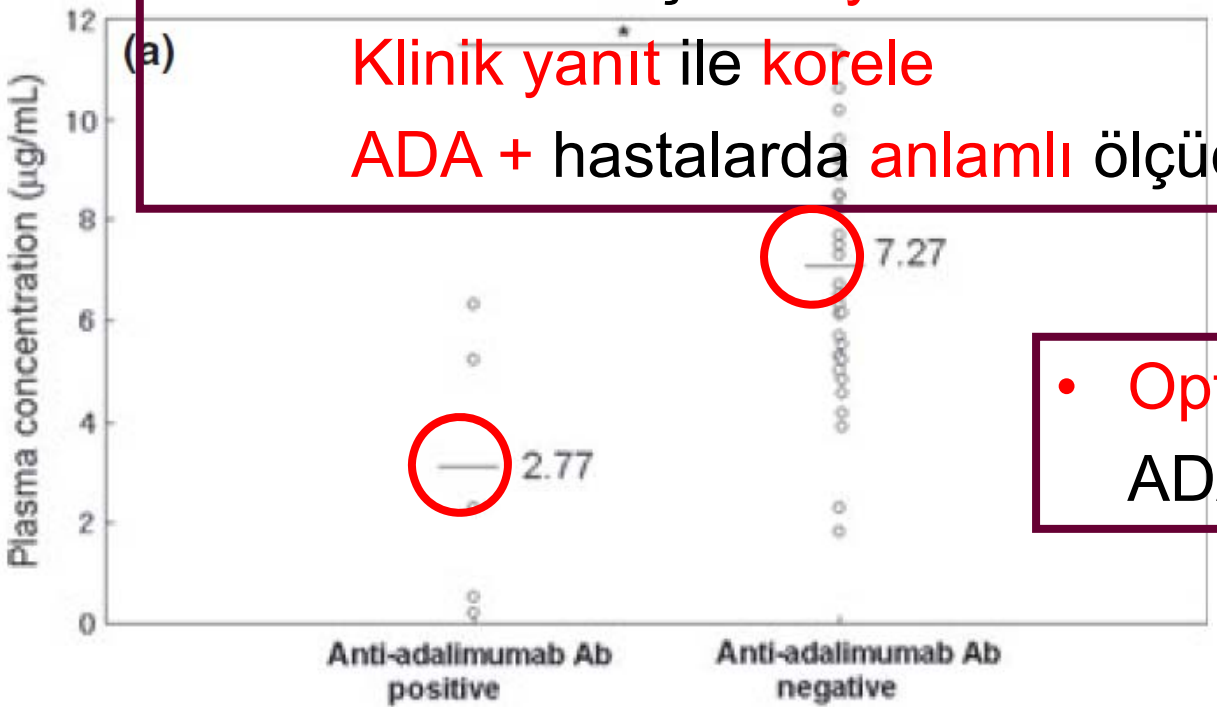
- ADAL ile tedavide 32 psoriasisli, 48.hafta
- İlaç düzeyleri ve ADA / PASI ile ilişki

- INF & ADAL ilaç düzeyi
  Klinik yanıt ile korele
  ADA + hastalarda anlamlı ölçüde düşük



- Optimal cut-off
  ADAL: >7.84 (>PASI75)

İmmünojenite: Kontrol mümkün mü?

- İlaç rejimini / uygulama yolunu değiştirmek
- İlacın dozunu arttırmak (sıklık dahil..)
- İmmünsupresif ilaç eklemek (MTX)

Carrascosa JM. Actas Dermosifiliogr 2013

Aralıklı & Kesintisiz tedavi

- Uygulama yolu (im, sc > iv, po)
- Düşük doz & aralıklı tedavi > Kesintisiz tedavi

  (İnfliksimab, RESTORE ve klinik deneyimler)

Carrascosa JM. Actas Dermosifiliogr 2013

Doz modifikasyonları

- ADA: Klirens artışı & düşük ilaç düzeyi
  - Doz artışı
  - Uygulama sıklığı artışı

- Daha yüksek ilaç dozlarına maruziyet☹
- Yüksek maliyet☹

Carrascosa JM. Actas Dermosifiliogr 2013

+ MTX

- Uygulama / Veri → Romatoloji > Dermatoloji

- RA, spA

  ADA gelişimi sıklığında a

  gelişimini geciktirm

Table 3 Meta-regression stratified by clinical characteristics to address the effect of ADA on drug response and the effect of IS on ADA detection

Clinical characteristic	RR (95% CI)	p for interaction
Effect of ADA on response		
Imunosupressors, %		
Lower proportion IS (<67%)	0.24 (0.11 to 0.53)	0.220
Higher proportion MTX (≥67%)	0.40 (0.27 to 0.61)	
Methotrexate, %		
Lower proportion MTX (<74%)	0.24 (0.14 to 0.40)	0.028
Higher proportion MTX (≥74%)	0.50 (0.35 to 0.71)	
Primary diagnosis		
RA	0.47 (0.33 to 0.65)	0.034
Other diseases	0.22 (0.12 to 0.40)	
Initiated higher biological doses		
No	0.47 (0.33 to 0.65)	0.034
Yes	0.22 (0.12 to 0.40)	
Dose escalation, %	0.31 (0.17 to 0.56)	0.57
Effect of IS on ADA detection		
Assay		
ELISAs	0.63 (0.50 to 0.79)	0.035
RIA	0.36 (0.23 to 0.57)	

ADA, anti-drug antibodies; ELISAs, Enzyme-linked immunosorbent assays; IS, immunosuppression; MTX, methotrexate; RA, Rheumatoid Arthritis; RIA, Radioimmuno assay; RR, Risk ratios.

Garces S, et al. Ann Rheum Dis 2012
Krieckaert CL, et al. Ann Rheum Dis 2012

+ MTX & Psoriasis

- Sınırlı çalışma / Hasta sayısı az
- 59 hasta ADAL

  26.hafta %45 ADA +

  5 hasta (+MTX) 1 hasta ADA +
- INF çalışması (TUR)

  ADA + hastalar

  + MTX ile ADA - / Klinik yanıtta düzelme
- İmmünsupresif etki > Sinerjistik etki

  Obezite & DM & alkolizm: PSO > RA

  Tedaviye destek amaçlı ☹ risk uygun mu?

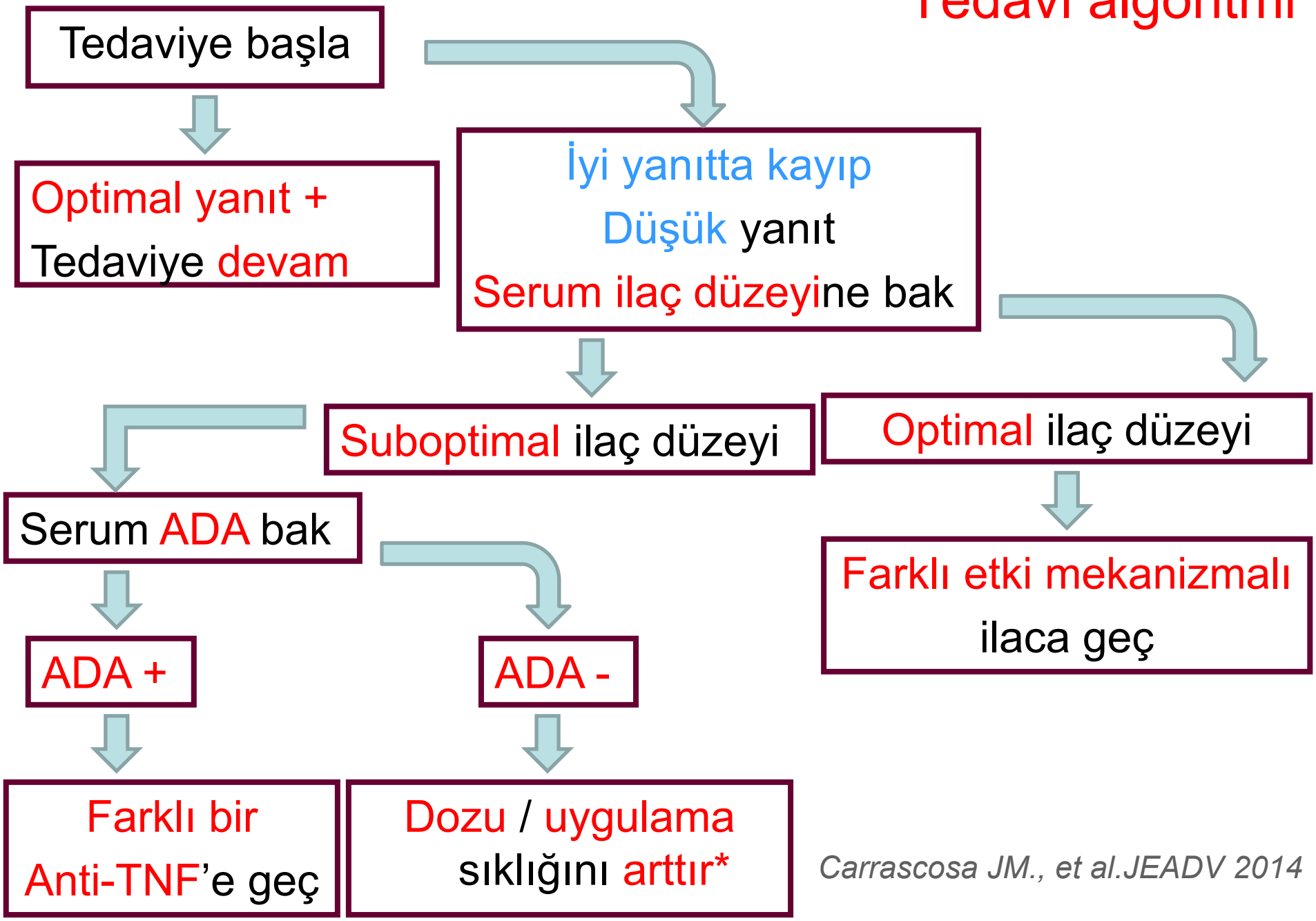
Menting S, et al. JEADV 2013
Adışen E, et al. J Dermatol 2010
Carrascosa JM. Actas Dermosifiliogr 2013

İmmünojenite izinde tedavi optimizasyonu

- 292 RA hastası / ETA
  - 203 Naive
    - 89 Önceden ADAL & INF
- 28. haftada değerlendirme
- En iyi klinik yanıt
  - Naive
  - Önceden ADAL & INF alanlardan ADA + olanlar
- Anlamlı kötü yanıt
  - Önceden ADAL & INF alanlardan ADA – olanlar
- ADA (-) anti-TNF yanıtsızlar başka ilaç grubuna!!

Jamnitski A, et al. Ann Rheum Dis 2011

Tedavi algoritmi



Carrascosa JM., et al.JEADV 2014

İmmünojenite & Mesajlar

- Eksojen maddelerin immün yanıt oluşturma yeteneği
- Ana mekanizma ADA gelişimi
  - Etkinlikte azalma / yanıt kaybı
  - Yan etki riskinde artış
  - Tedavide kalış süresinde / uyumda azalma
- Tedavi seçiminde / yönetimde önemli bir faktör
  - Biyolojikler değişken potansiyelde immünojen
- Klinik yanıt kaybında optimal yönetim için
  - Öncelikle ilaç düzeyi ± ADA testleri

Teşekkür ederim..