REUMAFLORENCE 2008

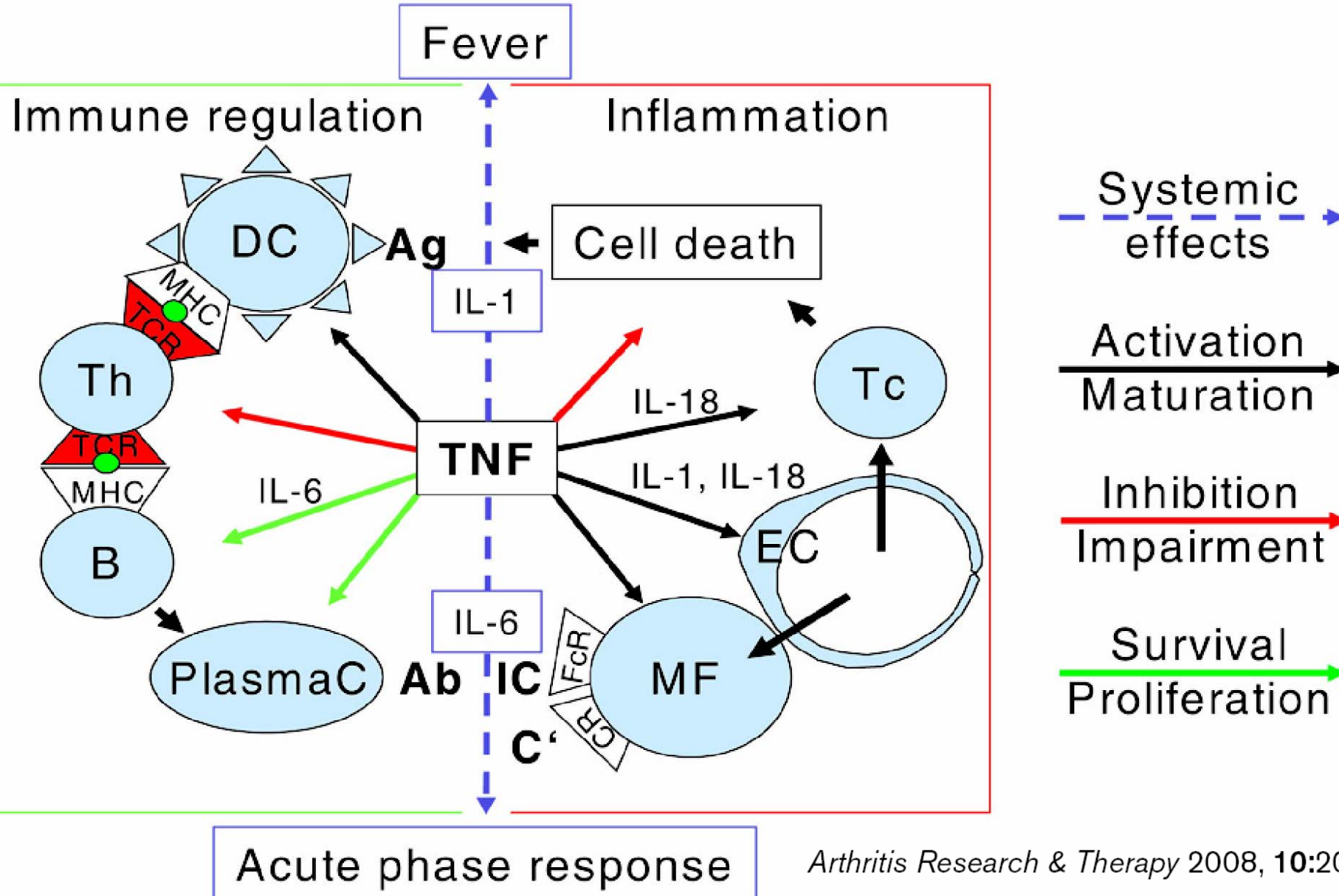
Le criticità della terapia biologica

"Induzione di autoanticorpi e lupus-like sindrome"

Lorenzo Emmi
Francesca Chiarini

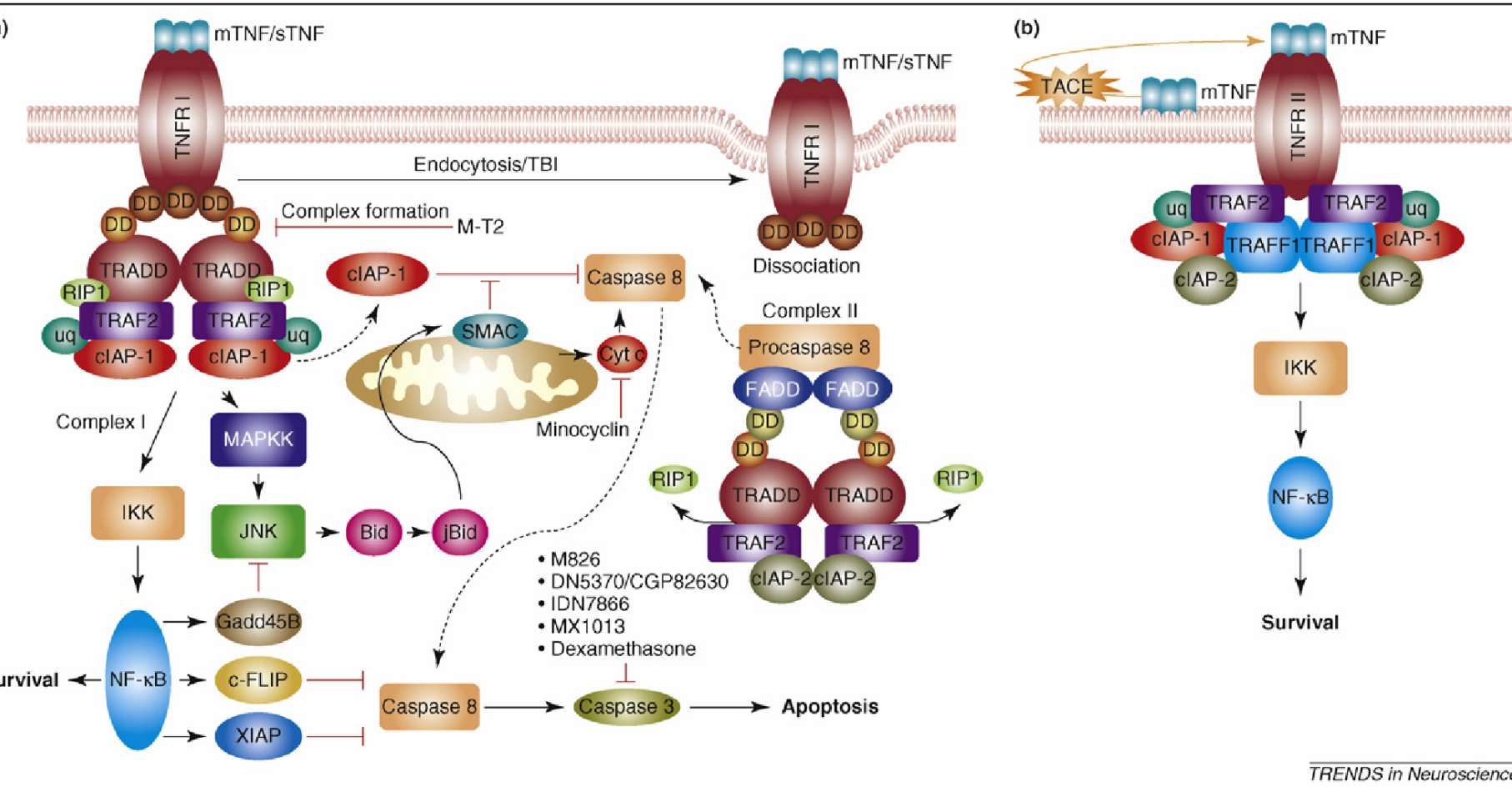
Centro di Riferimento Regionale per
le Malattie Autoimmuni Sistemiche

RUOLO DEL TNF-α NELLE RISPOSTE IMMUNOLOGICHE



Arthritis Research & Therapy 2008, **10**:20

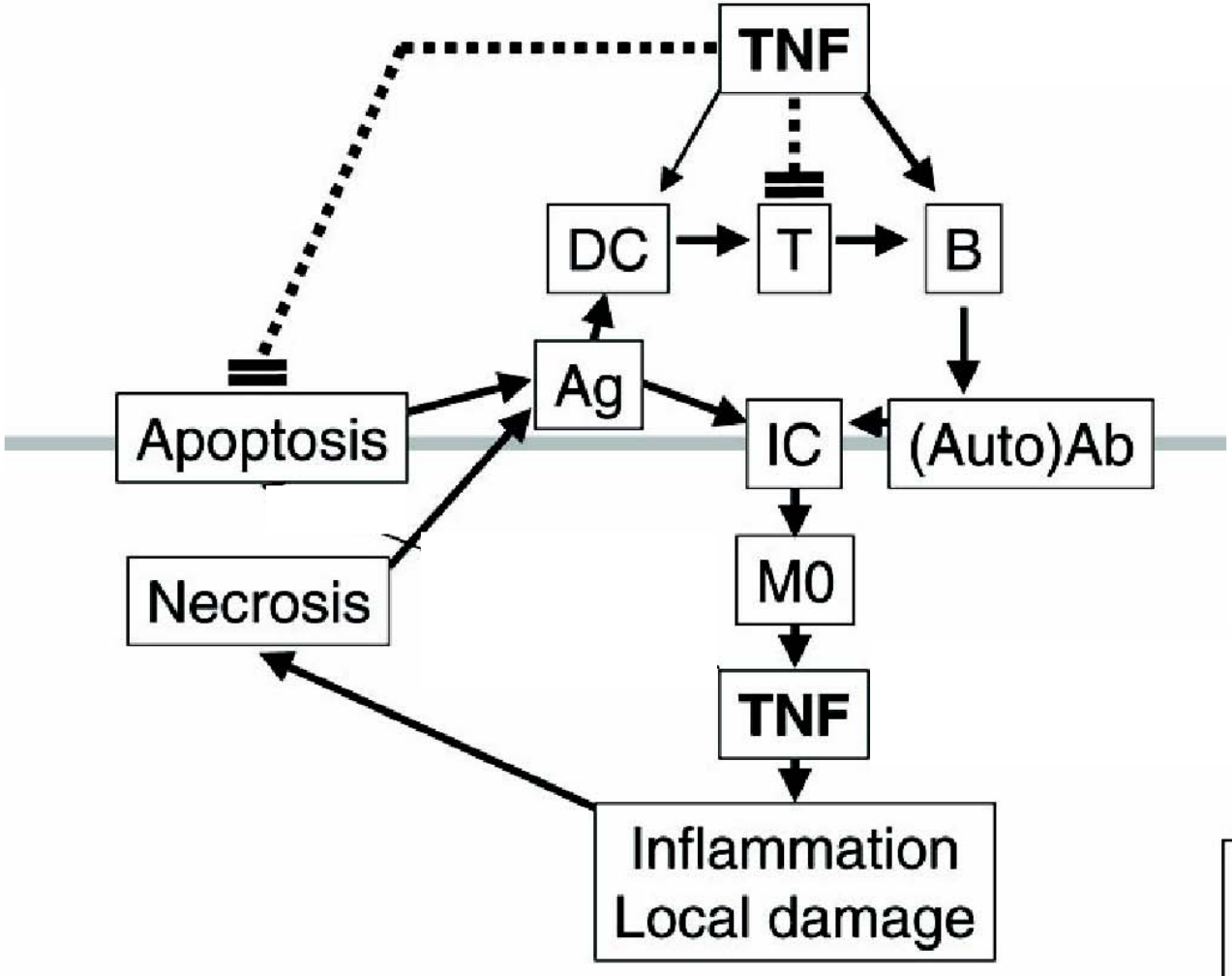
TNF/TNFR

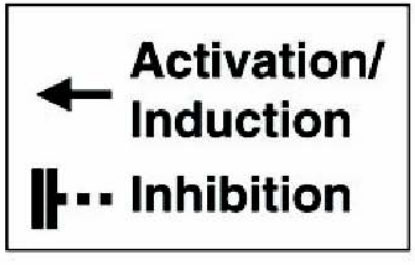


Trends in Neurosciences Vol.31 No.10 2008

POSSIBILI MECCANISMI ALLA BASE DELLA PRODUZIONE DI AUTOANTICORPI

RUOLO DEL TNF-α NEL LES





Arthritis Res Ther 2003, **5**:172-177

Topi NZB/NZW : ↓ TNF → LES

(sebbene la somministrazione di basse dosi di TNF-α a malattia conclamata acceleri la "renal disease")

LES ← TNF ↑ Topi MRL/lpr/lpr

Drug-induced lupus erythematosus

Giampiero Girolomoni et al. Arch Dermatol Res 2008

The mechanisms by which anti-TNFα therapy induces lupus remain unclear but are likely to differ from classic DILE.

One hypothesis could be the ability of the therapeutic anti-TNFα antibodies to bind to cell surface TNFα and to induce apoptotic cell death. This would then result in the release of antinucleosomal autoantigens and the induction of anti-dsDNA antibodies.

Another hypothesis is that the suppression of the T-helper type 1 response by TNF blockers could favour a T-helper type 2 response leading to SLE.

A final hypothesis is the role of bacterial infections which are increased with TNF blockers and are also powerful stimulants leading to polyclonal B-lymphocyte activation and autoantibody production.

Drug-induced lupus erythematosus

Giampiero Girolomoni et al. Arch Dermatol Res 2008

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One h Fα anti otic cell death. ucleosomal autoantigen

Ano -helper type 1 response by TNF e 2 response leading to SLE.

A final hypothesis is t e of ba ial infections which are increased with TNF blo rs and are also powerful stimulants leading to polyclonal B-lymphocyte activation and autoantibody production.

Ipotesi 1: giustificherebbe solo Lupus-Like da Infliximab

Ipotesi 2: TNF-α non è una citochina chiave nel "direzionamento" Th1 e d'altro canto non vi sono evidenze conclusive che il LES sia una malattia Th2

Ipotesi 3: le infezioni orientano il SI prevalentemente in senso Th1

Drug-induced lupus erythematosus

Giampiero Girolomoni et al. Arch Dermatol Res 2008

The mechanisms by which drugs induces lupus remain unclear. [illegible] SLE.

One hypothesis [illegible] TNF-α antagonists [illegible] apoptotic cell death. [illegible] nucleosomal autoantigens.

An alternative [illegible] T-helper type 1 response [illegible] type 2 response leading to [illegible]

A final [illegible] bacterial infections which are increased with [illegible] biologics and are also powerful stimulants leading to polyclonal B-lymphocyte activation and autoantibody production.

Inibizione TNF-α

IFN-γ → non blocco tro

Th1

IL-4, IL-10, IL-6

Ridotta espressione di CD 95

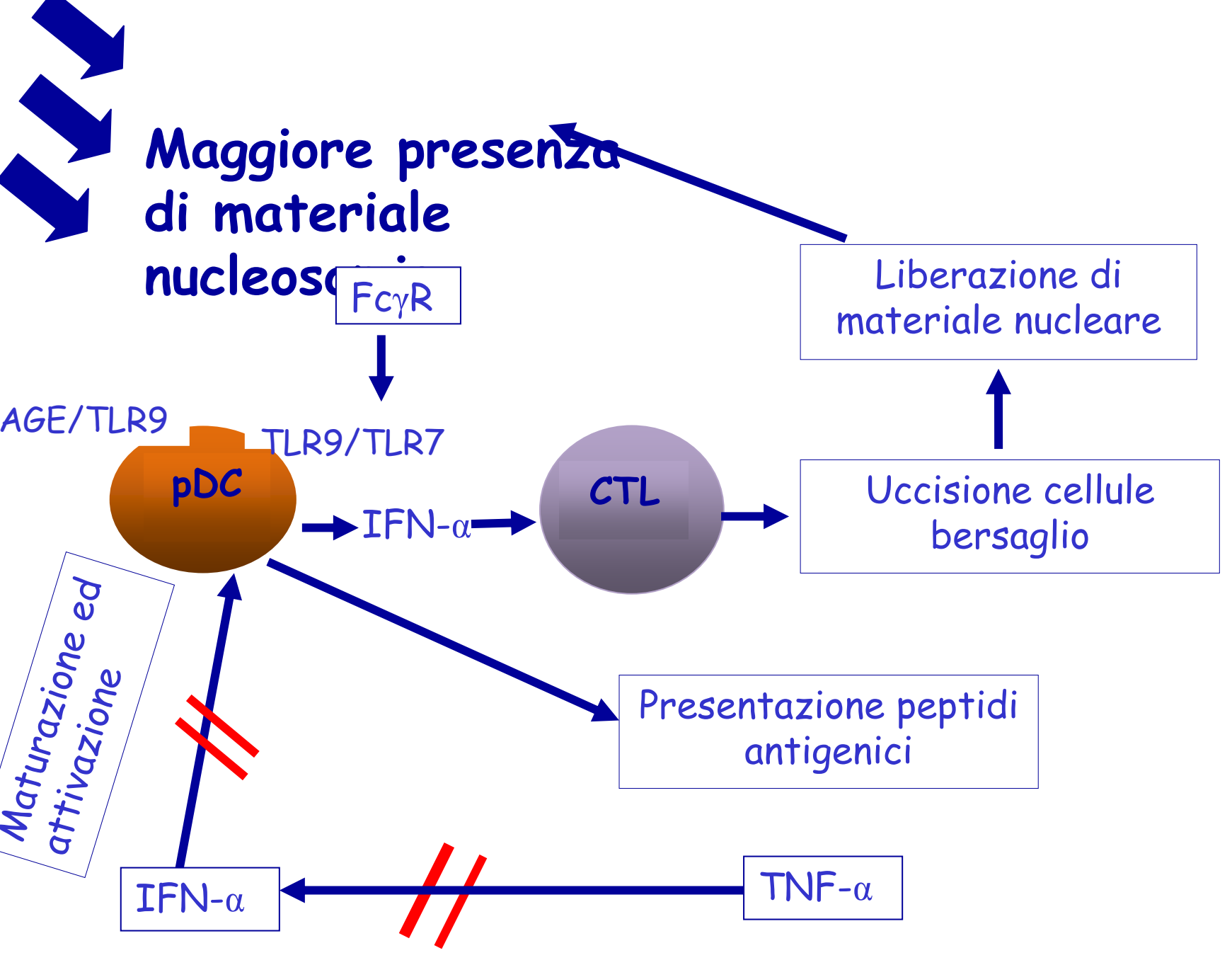
attività citolitica dei CTL

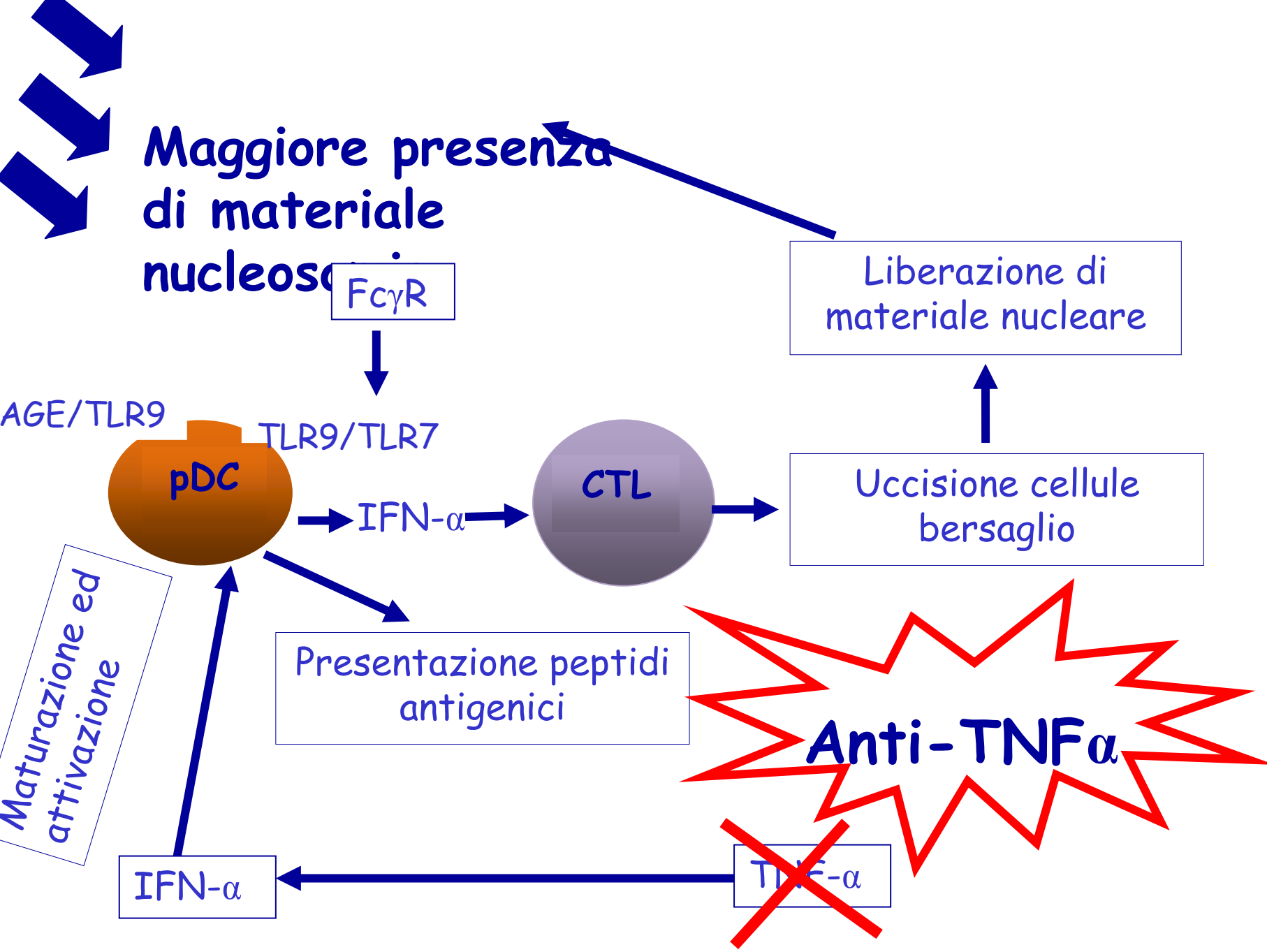
eliminazione cell. B autoreattive

Infliximab-induced lupus-like syndrome in a patient with ankylosing spondylitis

Hatice Bodur et al. Rheumatol Int 2008

Drug-induced lupus can be an adverse event in patients receiving anti-TNF α therapy. The etiopathogenesis of lupus development during this therapy is not accurately known yet. It is considered that TNF α upregulates the cellular expression of CD44 adhesion molecule. This molecule is involved in the phagocytosis of apoptotic neutrophils. Reduction of CD44 expression by anti-TNF α may potentially induce lupus by abnormal clearance and presentation of apoptotic material. Autoantibody formation is common in patients treated with anti-TNF α; nonetheless, clinical syndrome of lupus is rare. Therefore, it is considered that, among patients treated with anti-TNF α, lupus probably occurs in those with certain genetic and environmental predisposing factors for autoimmune disorders.


Maggiore presenza di materiale nucleos
FcγR
AGE/TLR9
TLR9/TLR7
pDC
IFN-α
CTL
Liberazione di materiale nucleare
Uccisione cellule bersaglio
Presentazione peptidi antigenici
Maturazione ed attivazione
IFN-α
TNF-α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Presentazione peptidi antigenici
Anti-TNFα
IFN-α
TNF-α

ANTI-TNF-α E COMPARSA AUTOANTICORPI

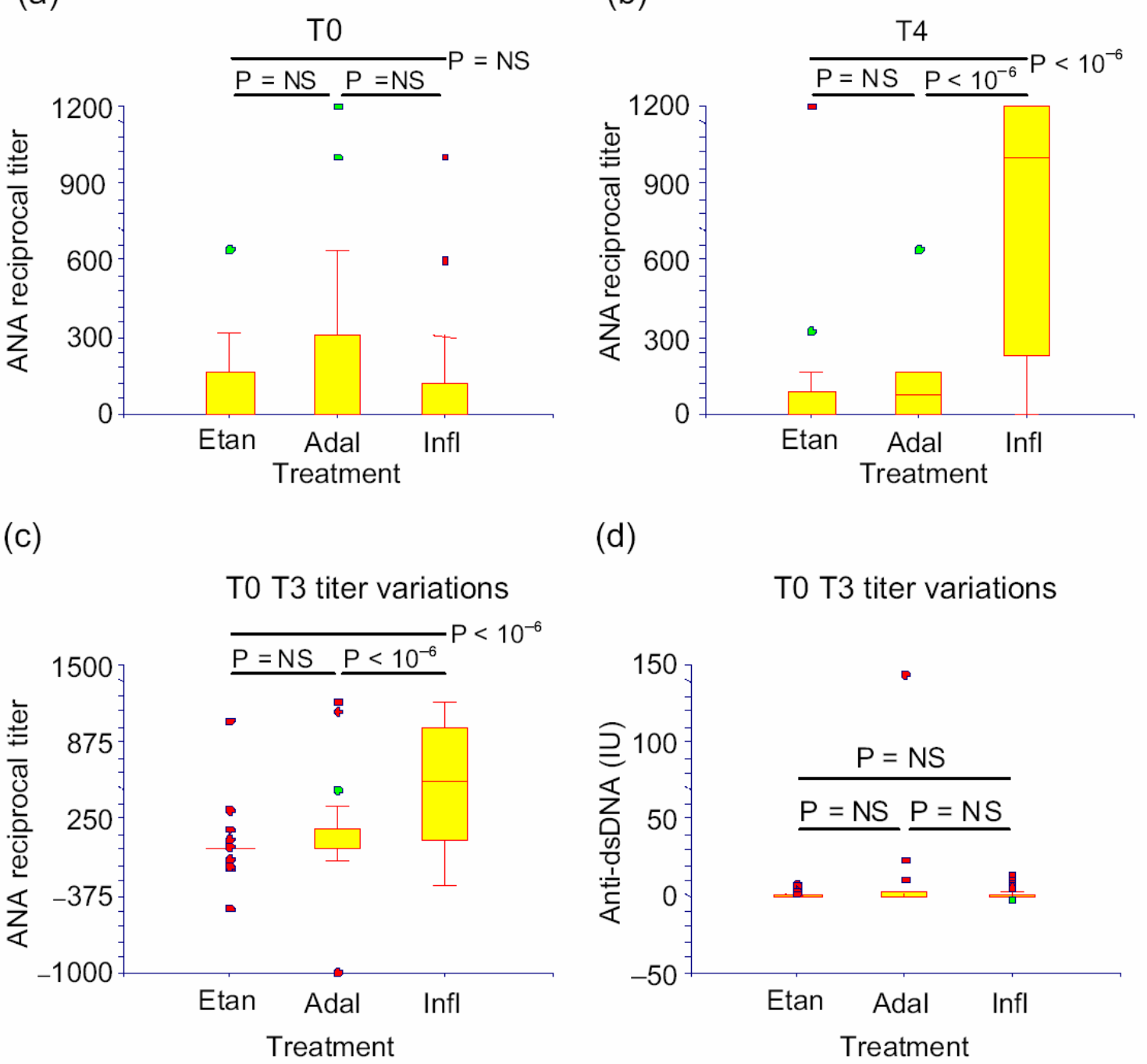
(Annals of the New York Academy of Sciences Vol.1051 2006)

	AR	MC
Infliximab		
ANA	63.8%	49,1%
ds-DNA	13%	21,5%
Etanercept		
ANA	11%	
ds-DNA	15%	
Adalimumab		
ANA	5.3%	
ds-DNA	12.9%	

Impact of Three Anti-TNFα Biologics on Existing and Emergent Autoimmunity in Rheumatoid Arthritis and Spondylarthropathy Patients

H. Bacquet-Deschryver · F. Jouen · M. Quillard · J. F. Ménard · V. Goëb · T. Lequerré · O. Mejjad · A. Daragon · F. Tron · X. Le Loët · O. Vittecoq

J Clin Immunol (2008) 28:445–455


(a)
T0
P = NS
P = NS
P = NS
1200
900
600
300
0
ANA reciprocal titer
Etan
Adal
Infl
Treatment
(b)
T4
P = NS
P < 10⁻⁶
P < 10⁻⁶
1200
900
600
300
0
ANA reciprocal titer
Etan
Adal
Infl
Treatment
(c)
T0 T3 titer variations
P = NS
P < 10⁻⁶
P < 10⁻⁶
1500
875
250
−375
−1000
ANA reciprocal titer
Etan
Adal
Infl
Treatment
(d)
T0 T3 titer variations
P = NS
P = NS
P = NS
150
100
50
0
−50
Anti-dsDNA (IU)
Etan
Adal
Infl
Treatment

LESSONS FOR LUPUS FROM TUMOUR NECROSIS FACTOR BLOCKADE

M De Bandt LUPUS 2006

As there are no recognized criteria for drug induced lupus we considered diagnosis in the case of: 1) a patient with anti-TNF alpha treatment for inflammatory arthritis, 2) temporal relationship between clinical manifestations and anti-TNF alpha treatment, 3) presence of at least four ACR criteria[37,38] of SLE, 4) musculoskeletal symptoms were taken into account only if they reappeared with other lupus symptoms in a patient in whom they had previously disappeared under anti-TNF therapy, 5) isolated positive results for anti-nuclear antibodies (ANA) or anti-dsDNA antibodies were not considered for diagnosis, given their high frequency in patients receiving this therapy

LESSONS FOR LUPUS FROM TUMOUR NECROSIS FACTOR BLOCKADE

M De Bandt LUPUS 2006

As there are no recognized criteria for drug induced lupus we considered diagnosis in the case of: 1) a patient with anti-TNF alpha treatment for inflammatory arthritis, 2) temporal relationship between clinical manifestations and anti-TNF alpha treatment, 3) presence of at least four ACR criteria[37,38] of SLE, musculoskeletal symptoms taken ac... if they reappeared with ... patient in whom th... anti-TNF ther... ti-nuclear antibodi... ...SDNA antibodies were not considered fo... diagnosis given their high frequency in patients rece... this therapy.

In our experience signs of lupus occurred after a mean of nine months (range 3–16) in patients treated with Infliximab and four months (range 2–5) in patients treated with etanercept. In all cases after diagnosis was determined, anti-TNF was stopped and specific treatment introduced (steroids). Lupus

Autoimmune Diseases Induced by TNF-Targeted Therapies

Analysis of 233 Cases

Manuel Ramos-Casals, MD, PhD, Pilar Brito-Zerón, MD, PhD, Sandra Muñoz, MD, Natalia Soria, MD, Diana Galiana, MD, Laura Bertolaccini, MD, PhD, Maria-Jose Cuadrado, MD, PhD, and Munther A. Khamashta, MD, PhD

(*Medicine* 2007;86:242–251)

Registry of Autoimmune Diseases Associated With Anti-TNF Agents*

Disease	Total No. of Cases Reported
Cutaneous leukocytoclastic vasculitis	79
Lupus-like syndrome	48
Systemic lupus erythematosus	37
Interstitial lung disease	18
Cutaneous necrotizing vasculitis	8
Isolated cutaneous lupus	7
Peripheral neuropathy	6
Rapidly progressive glomerulonephritis	5
Cutaneous lymphocytic vasculitis	4
Sarcoidosis	3
Henoch-Schönlein purpura	2
Pulmonary hemorrhage	2
Inflammatory myopathies	2
Antiphospholipid syndrome	2
Polyarteritis nodosa	1
Temporal arteritis	1
Urticarial vasculitis	1
Bronchiolitis obliterans organizing pneumonia	1
Other type of vasculitis	6
Total	**233**

*Last update: December 31, 2006.

Feature	Anti-TNF-Related Lupus (%)	Procainamide-Related Lupus (%)	Idiopathic SLE (%)
ANA	79	>95	99
Anti-dsDNA	72	<5	90
Rash/cutaneous involvement	67	<5	54–70
Arthritis	31	20	83
Fever/general symptoms	23	45	42
Hypocomplementemia	17	<5	48
Leukopenia	14	15	66
Serositis	12	50	28
aCL	11	5–20	15
Glomerulonephritis	7	<5	34
Thrombocytopenia	6	<5	31
Neuropsychiatric	3	<5	12
Anti-histone antibodies	ND	>95	50–60

Abbreviations: aCL = anticardiolipin antibodies; ND = no data.

FATTORI PREDITTIVI DI LUPUS-LIKE SYNDROME

- Polimorfismo genetico TNF-α
- Presenza prima del trattamento di anticorpi antinucleari
- Comparsa di anticorpi anti-nucleosomi
- L'isotipo dell' anticorpo

Recommendations for the Management of Autoimmune Diseases Associated With Anti-TNF Agents

1. Perform baseline immunologic analysis and chest X-ray upon starting anti-TNF therapy.
2. Maintain specific follow-up centered on the possible development of cutaneous, articular, or pulmonary manifestations.
3. Evaluate adverse effects related to anti-TNF accurately, discarding the existence of undiagnosed autoimmune diseases (mainly systemic vasculitis, lupus, or ILD).
4. In patients with mild features (cutaneous, articular, and/or general involvement), cessation of anti-TNF therapy will probably be sufficient, although continuation might be considered under close follow-up.
5. In patients with severe (pulmonary, renal, or neurologic) involvement, cessation of anti-TNF therapy is mandatory, probably together with corticosteroids (adding immunosuppressive agents according to the clinical evolution).
6. Preexisting SLE, especially in the presence of severe organ involvement (renal, pulmonary, or neurologic), should be considered as a precautionary scenario for the use of anti-TNF agents.
7. Anti-TNF agents should not be used in patients with preexisting interstitial pulmonary disorders.

Autoimmune Diseases Induced by TNF-Targeted Therapies
Analysis of 233 Cases
(*Medicine* 2007;86:242–251)

Review

The role of tumor necrosis factor-alpha in systemic lupus erythematosus

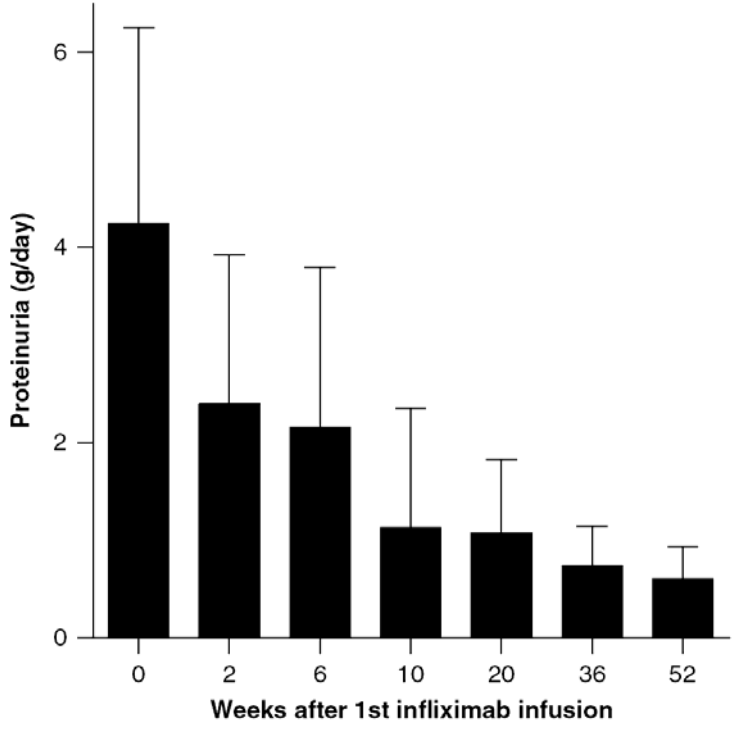
Martin Aringer[1] and Josef S Smolen[2]

Arthritis Research & Therapy 2008, **10**:202

Efficacy and safety of TNF-blocker therapy in systemic lupus erythematosus

Martin Aringer† & Josef S Smolen

Expert Opin. Drug Saf. (2008) 7(4):411-419



CONCLUSIONI

- Prima di intraprendere terapia con anti-TNF-α è necessaria un' attenta valutazione clinica ed immunologica del paziente;
- E'consigliabile la determinazione degli autoanticorpi (ANA,anti-ENA,anti-DNA) al tempo zero e periodicamente durante il trattamento;
- L'approccio terapeutico, nonché il prosieguo della terapia, si deve basare sul quadro clinico. In particolare la comparsa di lieve sintomatologia può indurre ad una pausa nella somministrazione della terapia, mentre un importante coinvolgimento d'organo impone la sospensione del trattamento;
- La comparsa di autoanticorpi è frequente, mentre è rara l'evenienza di una sindrome Lupus-like