



ROMA, 6-7 APRILE 2018

**PRINCIPI ed
AGGIORNAMENTI
in DERMATOLOGIA**

NH Hotel Vittorio Veneto - Corso d'Italia 1, 00198 Roma

Responsabili scientifici
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L'ERA DEGLI ANTI-TNF- α



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Psoriasis & Anti-TNF- α



Table 1
Registration dates for biological therapies in psoriasis (FDA & EMA)

Nonproprietary Name	Proprietary Name	US FDA Regulatory Approval for Psoriasis ^a	EU EMA Regulatory Approval for Psoriasis ^a
Alefacept ^b	Amevive ^b	Jan 2003	Not registered
Efalizumab ^b	Raptiva ^b	Oct 2003	June 2004
Etanercept	Enbrel	May 2004	Sept 2004
Infliximab	Remicade	Sept 2006 ^c	Oct 2005
Adalimumab	Humira	Jan 2008	Dec 2007
Ustekinumab	Stelara	Sept 2009	Jan 2009

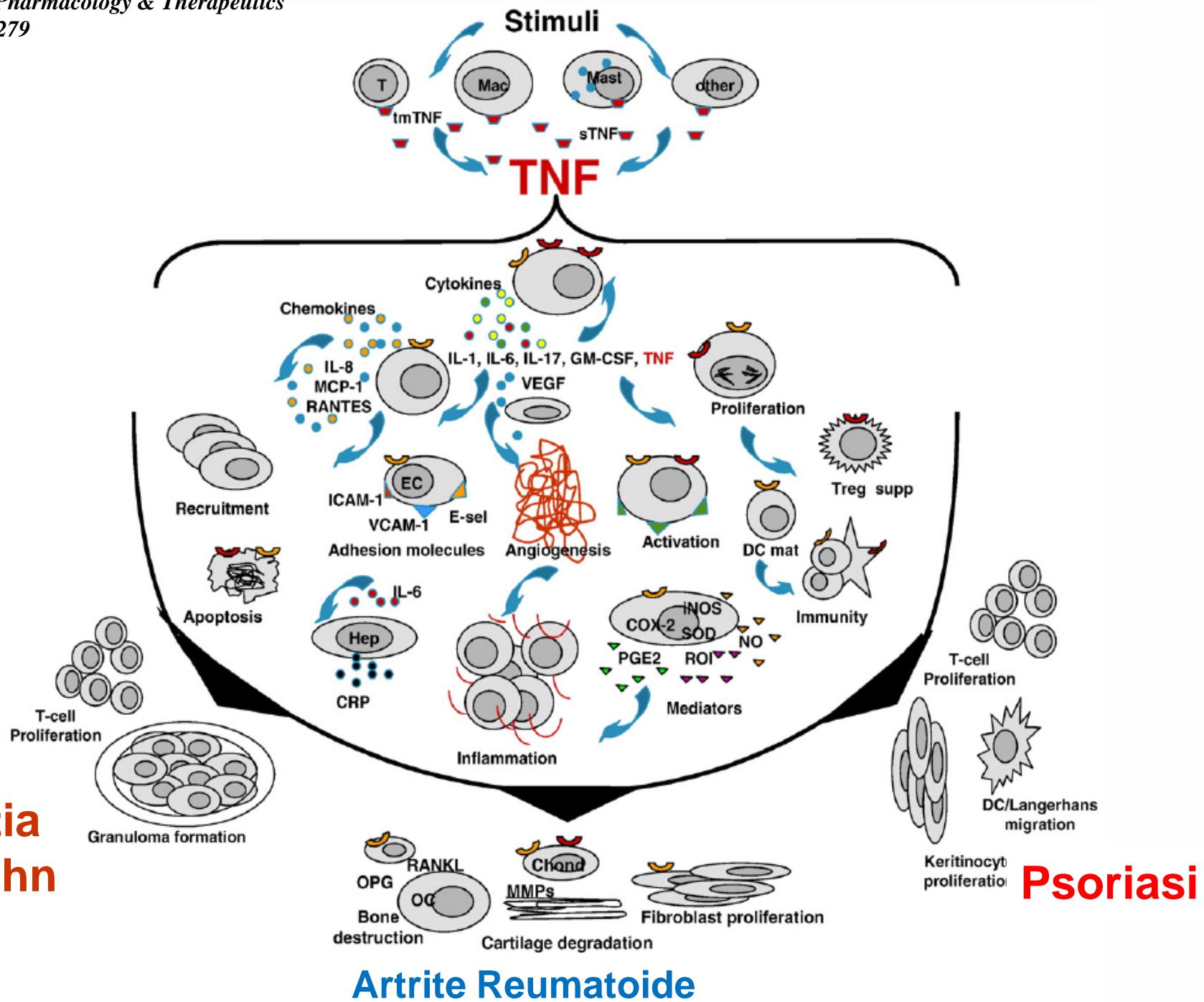
TNF- α citochina chiave nella Psoriasi

Aumentata espressione:

- Cute
- Articolazioni
- Siero (correla con attività)

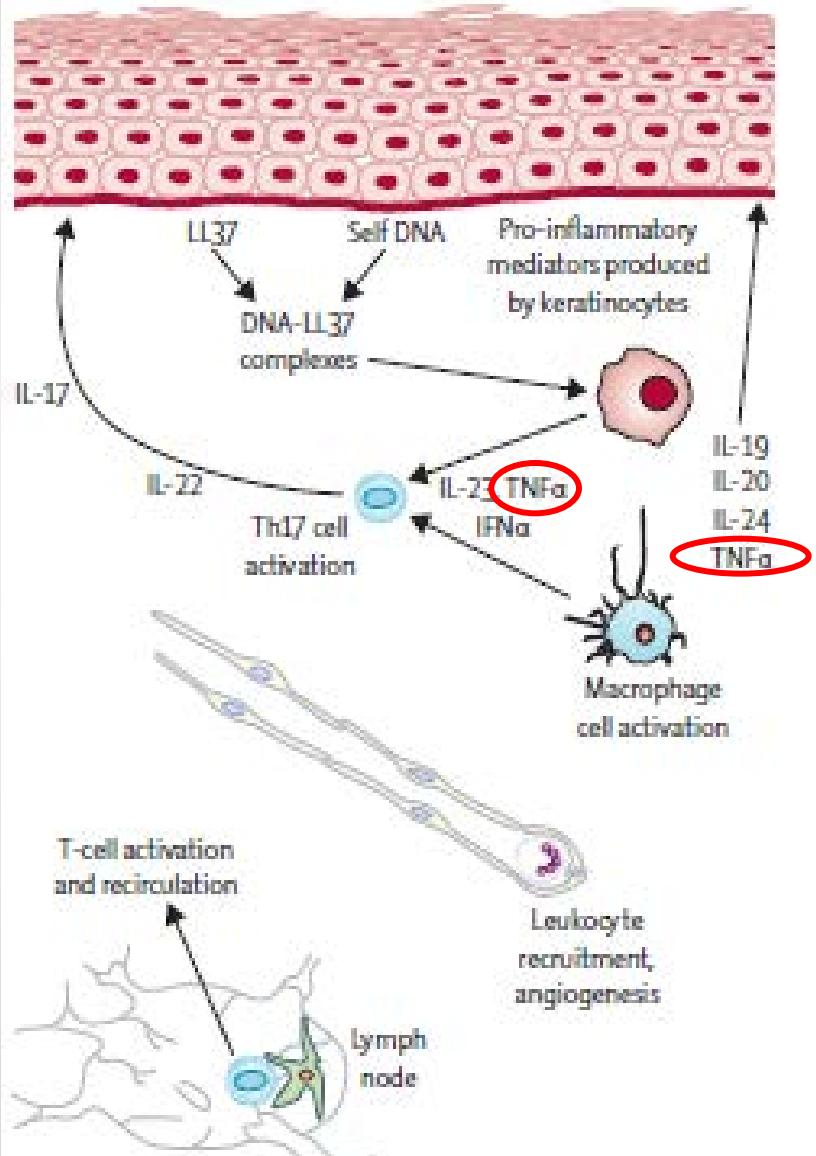
Prodotto da: Cheratinociti, Cellule Dendritiche, NKT, Th1, Th17, Th22, Macrofagi, Mastociti

Recettori TNF su: Cheratinociti, Neutrofili, Cellule Endoteliali, Fibroblasti

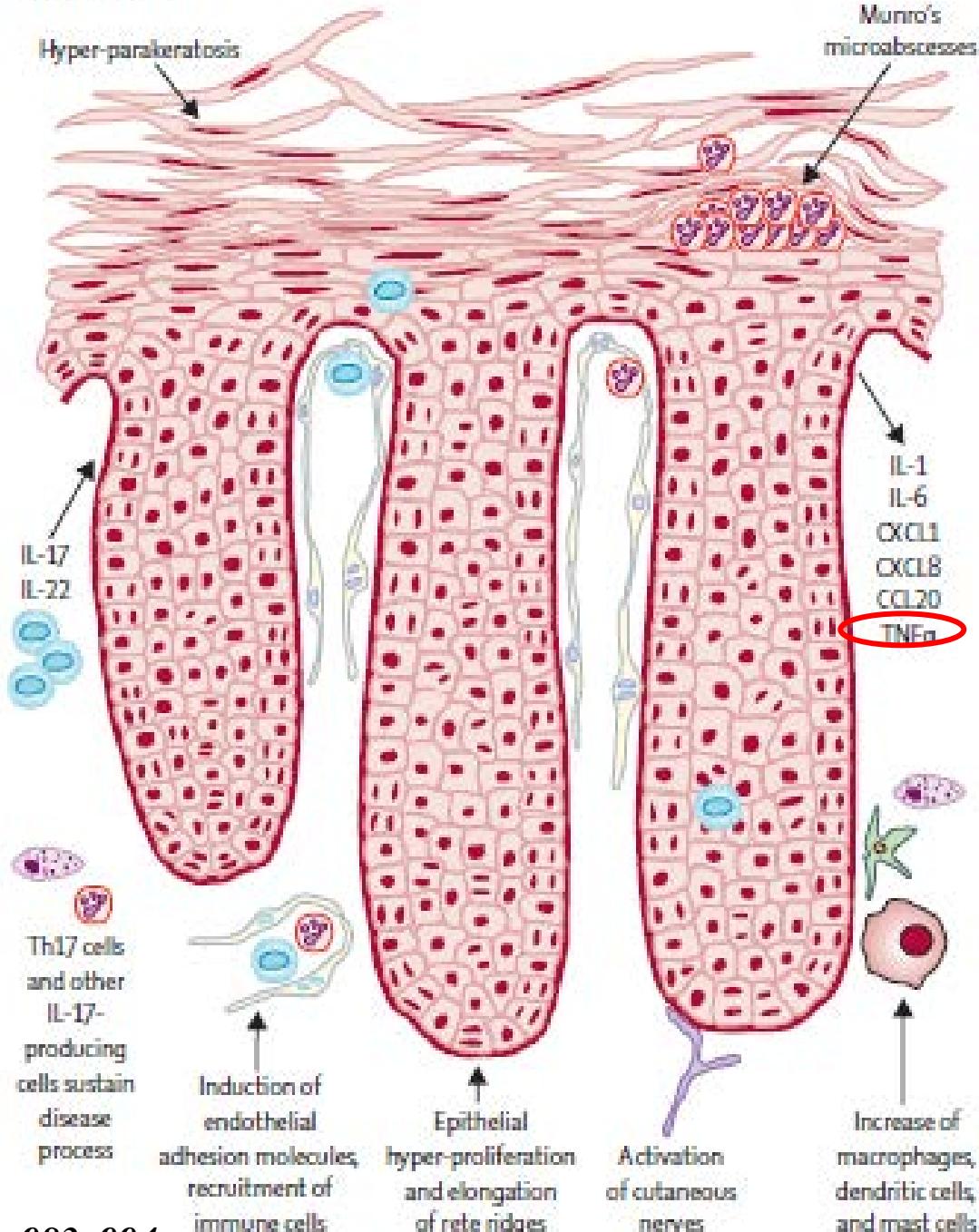


A Pre-psoriatic skin

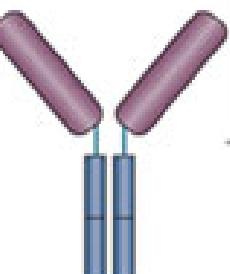
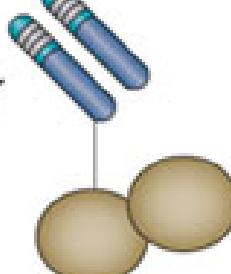
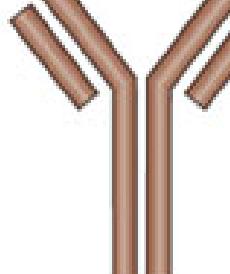
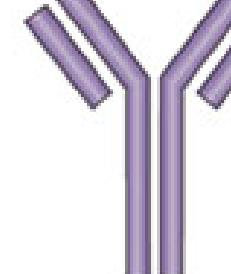
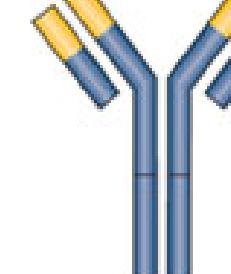
TNF- α nella Psoriasi



B Psoriatic skin



Psoriasis & Anti-TNF- α

Etanercept	Certolizumab pegol	Adalimumab	Golimumab	Infliximab
 [TNF receptor]				 [(Fab') ₂] [Fc region]
100% Human Human TNFRp75 Fusion protein	80% Human Peg-Humanized Fab mAb	100% Human Human mAb	100% Human Human mAb	75% Human Chimeric mAb
SC	SC	SC	SC	EV
50 mg/sett	200 mg/2 sett	40 mg/2 sett	50 mg/4 sett	5mg/Kg/8 sett
Pso e PsA	+ Mtx	Pso e PsA	\pm Mtx	
Pso ped	PsA	Pso ped	PsA	Pso e PsA

ATTRACTIVE OPPORTUNITIES FOR BIOSIMILAR PRODUCERS

	2014 US SALES	MAIN INDICATION(S)	BIOSIMILAR CHALLENGERS
abbvie  HUMIRA	US\$ 7.22 BILLION	RA, JIA, ankylosing spondylitis, plaque psoriasis, psoriatic arthritis, Behcet's syndrome, Crohn's disease, ulcerative colitis	     SAMSUNG BIOEPIS
AMGEN®  ENBREL	US\$ 5.51 BILLION	RA, JIA, ankylosing spondylitis, plaque psoriasis, psoriatic arthritis	  
Johnson & Johnson  REMICADE	US\$ 4.50 BILLION	RA, ankylosing spondylitis, Crohn's disease, plaque psoriasis, psoriatic arthritis, ulcerative colitis, Behcet's syndrome	   SAMSUNG BIOEPIS

Biologici: Indicazioni

FARMACO	Target	Pso	PsA	HS	RA	Spon	jIA	Cro	UC
ADALIMUMAB	TNF-α	X	X	X	X	X	X	X	X
CERTOLIZUMAB P	TNF-α		X		X	X			
ETANERCEPT	TNF-α	X	X		X	X	X		
GOLIMUMAB	TNF-α		X		X	X	X		X
INFliximab	TNF-α	X	X		X	X		X	X
USTEKINUMAB	IL-12/23	X	X						
SECUKINUMAB	IL-17A	X	X			X			
IXEKIZUMAB	IL-17	X							
RITUXIMAB	CD-20				X				
ANAKINRA	IL-1R				X				
ABATACEPT	CD-80/86				X		X		

Off-label in Dermatologia

Aftosi Complessa

Psoriasis Pustolosa

Malattia di Behçet

Psoriasis Eritrodermica

Acne Conglobata

Orticaria Cronica

Pioderma Gangrenoso

Malattia di Sweet

Sarcoidosi

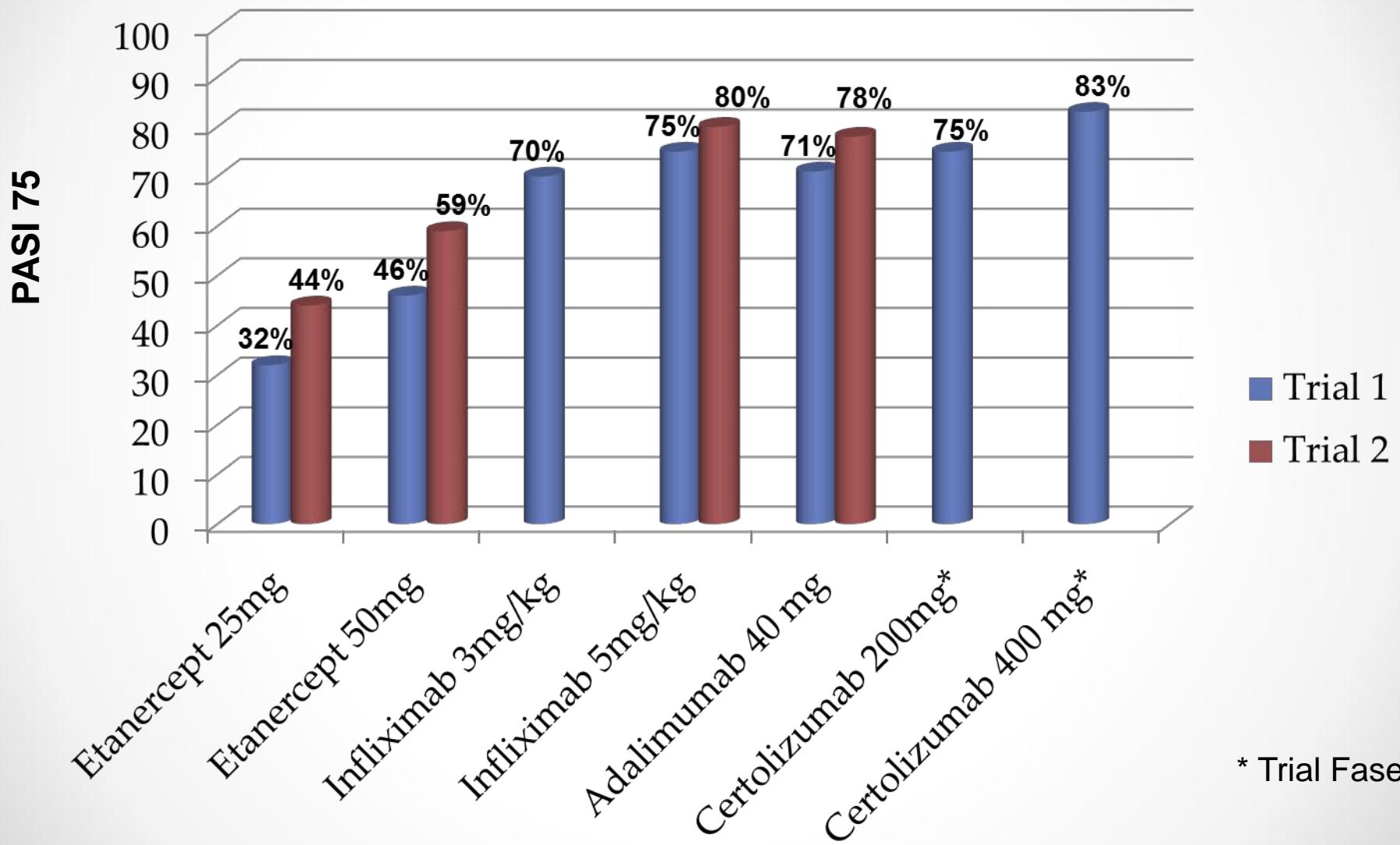
Granulomatosi Orofaciale



Levin EC et al. J Drugs Dermatol. 2014; 13(3):342-354

Sand FL, Thomsen SC. Dermatol Ther. 2015; 28: 158–165

Efficacia Anti-TNF- α nella Psoriasi



* Trial Fase 2

See related article on pg 1638

Does Treatment of Psoriasis Reduce Cardiovascular Comorbidities?



CrossMark

Mark Lebwohl¹

Psoriasis has been associated with an increase in myocardial infarctions. Several registries have shown reductions in major adverse cardiovascular events in psoriasis patients and rheumatoid arthritis patients treated with tumor necrosis factor- α antagonists. Many assume that the reduction in cardiovascular events can be attributed to the anti-inflammatory effect of tumor necrosis factor blockers, but a 52-week study conducted by Bissonnette and coworkers failed to show a reduction in cardiovascular inflammation in psoriasis patients treated with adalimumab. Longer and larger studies are needed to explain why tumor necrosis factor- α blockade appears to reduce cardiovascular events in patients with severe psoriasis.

Journal of Investigative Dermatology (2017) 1

Clinical Implications

- Severe psoriasis has been associated with an increase in myocardial infarctions.
- In many registries, the use of TNF- α blockers is associated with a large reduction in the frequency of myocardial infarctions in patients with severe psoriasis.
- A 52-week study of adalimumab in patients with psoriasis failed to show a reduction in cardiovascular inflammation.

Scelta del Farmaco

La scelta del farmaco è un processo complesso che deve tenere conto di...

- Evidence-based medicine (linee guida, etc)
- Caratteristiche farmaco
- Esperienza
- Caratteristiche del paziente
- Contesto normativo locale

Anti-TNF- α in Psoriasi

INFILIXIMAB: - onicopatia psoriasica severa
- comorbidità infiammatorie
- gestione dosaggio

ADALIMUMAB: - comorbidità infiammatorie (PsA ++)
- psoriasis pediatrica

ETANERCEPT: - comorbidità infiammatorie
- comorbidità infettive
- psoriasis pediatrica

GOLIMUMAB: - approvato per PsA ma efficace anche su Pso

CERTOLIZUMAB P: - approvato per PsA ma efficace anche su Pso
- gravidanza

INFliximab

**Anticorpo monoclonale anti-TNF-a
chimerico umano-murino di classe IgG1 (149 KDa)**



Approvato per Pso e PsA dal 2006

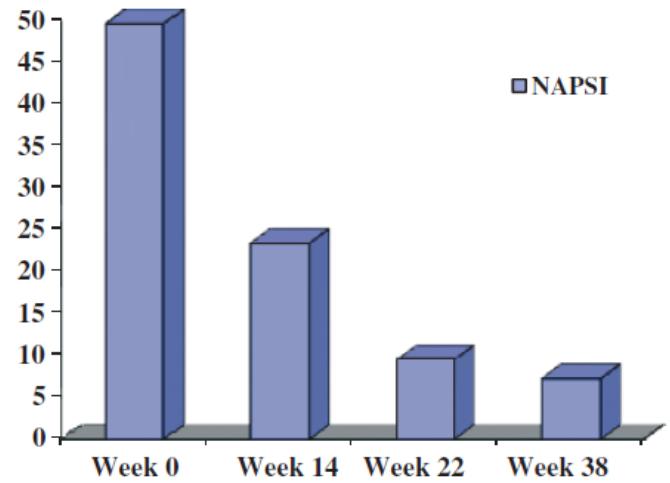
- ✓ Lega TNF-a solubile e di membrana con elevata affinità ($K_a = 10^{10} \text{ M}^{-1}$) e specificità
- ✓ Induce l' apoptosi di LT attivati e di macrofagi
- ✓ Complessi altamente stabili
- ✓ Marcata induzione di apoptosi
- ✓ Emivita: 9.5 giorni
- ✓ Infusione e.v. lenta, 5 mg/Kg 0, 2, 6 sett., poi ogni 8 sett

Il primo anticorpo monoclonale terapeutico usato nel 1998 per il trattamento di malattie infiammatorie (morbo di Crohn)

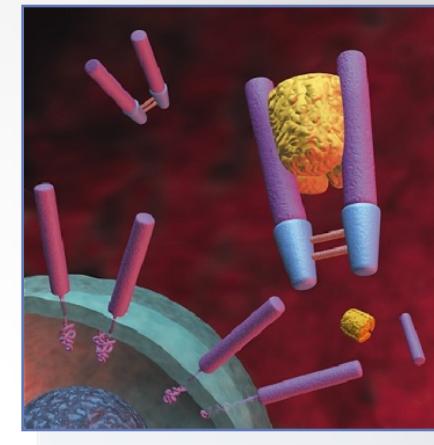
INFliximab

Risposta Clinica: 1-2 settimane

Efficacia: $\geq 80\%$ raggiunge PASI 75



ETANERCEPT



**Proteina di fusione:
dimero della porzione extracellulare del
recettore p75 per il TNFa associato al frammento
Fc di una IgG1 umana (150 KDa)**

Approvato per Pso e PsA dal 2004

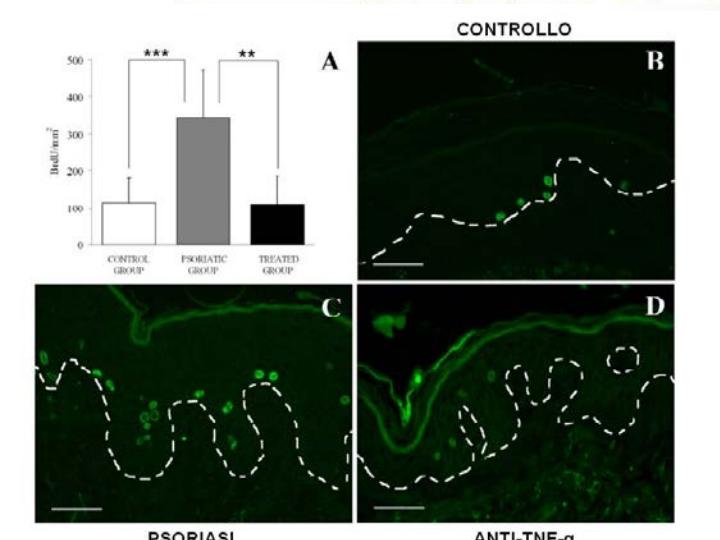
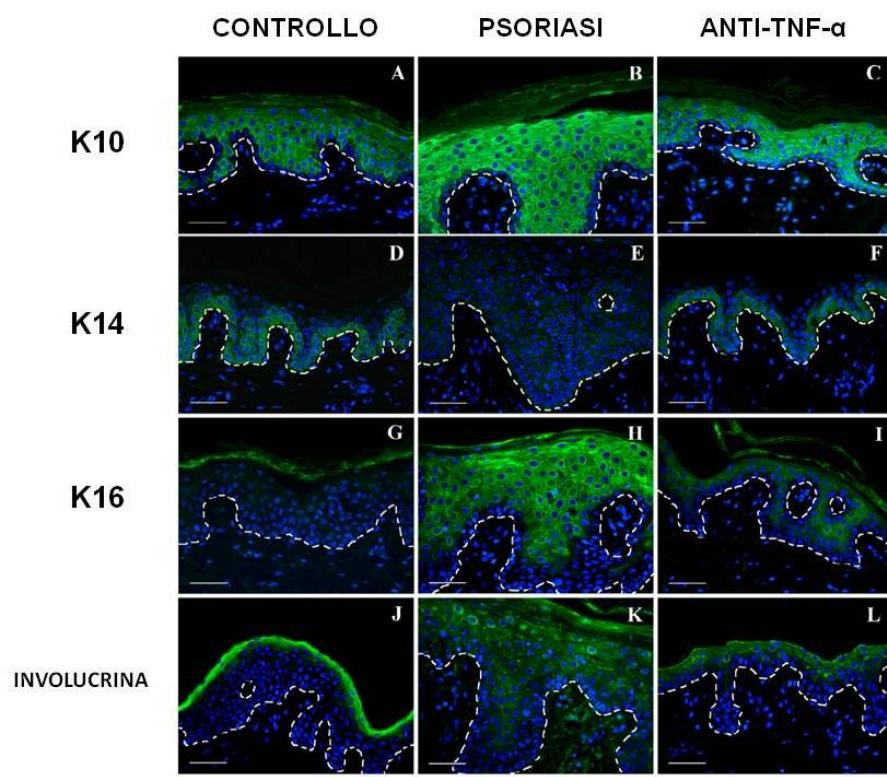
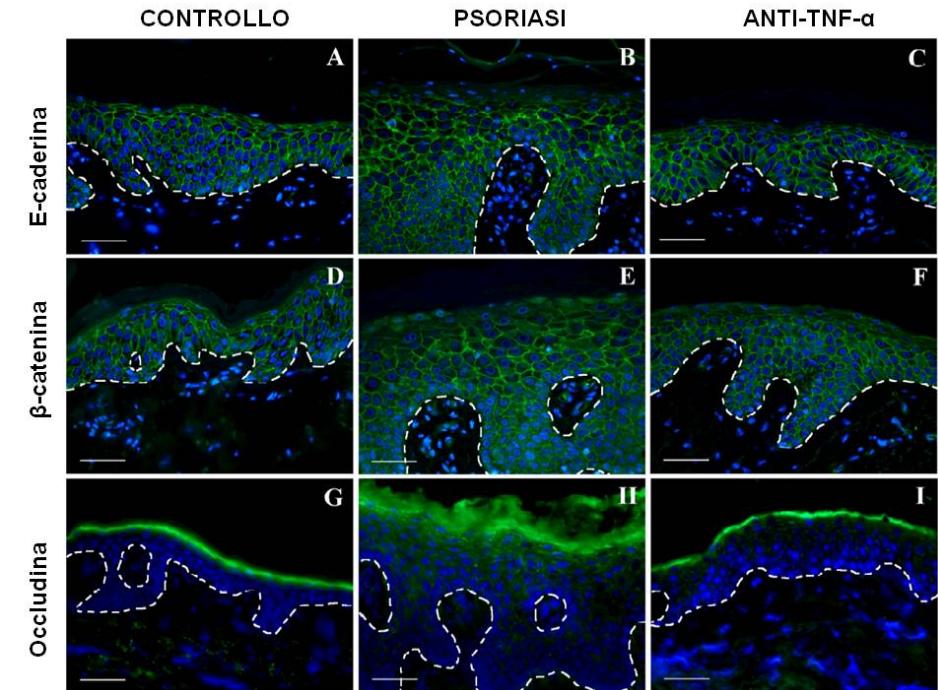
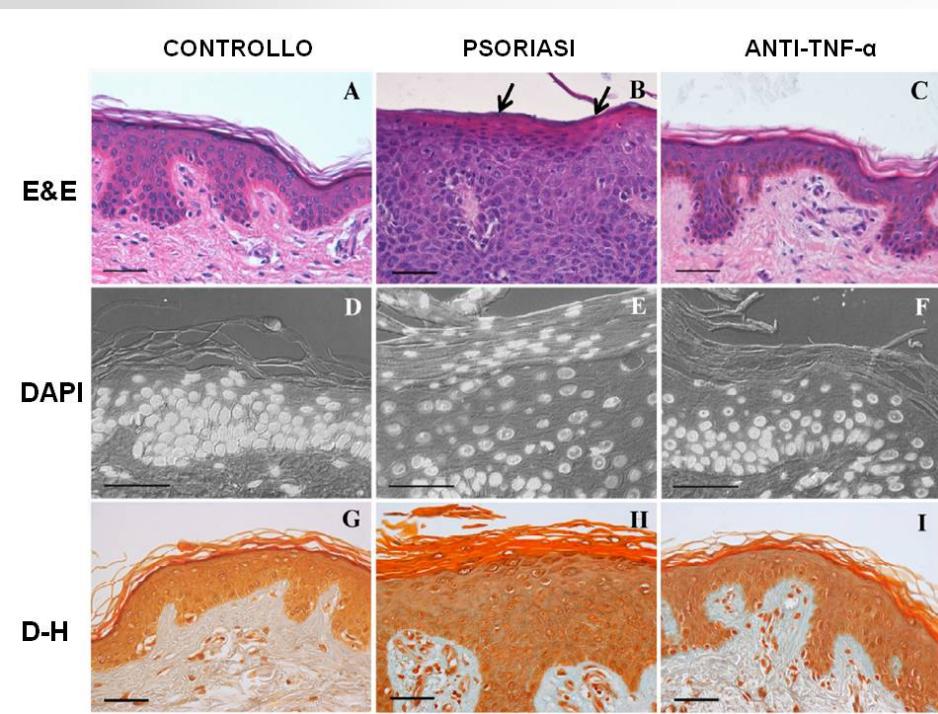
- ✓ Lega e neutralizza sia TNF-a che TNF-b (linfotossina)
solubili e di membrana
- ✓ Affinità di legame con TNF-a: moderata-alta ($K_a = 10^{10} \text{ M}^{-1}$)
- ✓ Il legame è reversibile, il TNF dissociato rimane bioattivo
- ✓ Eliminazione: 3-5,5 giorni
- ✓ Somministrazione: via sottocutanea 25 x 2/w - 50 mg x 1-2/w
- ✓ **Indicazione pediatrica** (> 8 anni): **0.8 mg/kg**
- ✓ In monoterapia o in associazione con Metotrexato (PsA), Acitretina e UVB/bs

ETANERCEPT

Risposta Clinica: 6-12 settimane (max 34 settimane)

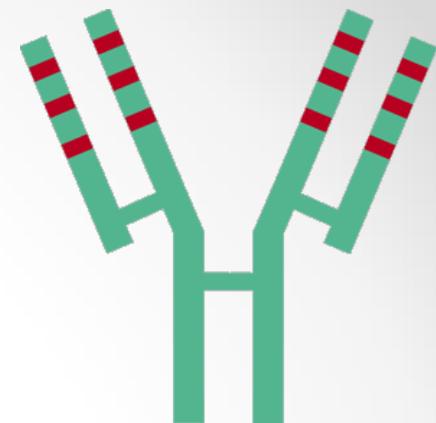
Efficacia: 34% (25x2), 38% (50x1), 49% (50x2) raggiunge PASI 75





Donetti E, Gualerzi A, Ricceri F, Pescitelli L, Bedoni M, Prignano F. Exp Dermatol. 2012; 21(7):549-551.

ADALIMUMAB



Anticorpo monoclonale anti-TNF- α umano (148 KDa)

Approvato per Pso e PsA nel 2007

- ✓ Alta affinità e selettività per il TNF- α (no TNF- β)
- ✓ Lega e neutralizza sia il TNF solubile che di membrana
- ✓ Elimina: 10-20 giorni
- ✓ Somministrazione per via s.c.: carico di 80 mg al tempo 0, 40 mg alla settimana 1, poi 40 mg ogni 2 settimane

ADALIMUMAB

Risposta Clinica: 4-8 settimane (max 16 settimane)

Efficacia: 59% raggiunge PASI 75



GOLIMUMAB

Anticorpo monoclonale anti-TNF- α umano (148 KDa)

Approvato per PsA nel 2009

Somministrazione per via s.c. 50 mg ogni 4 settimane (\pm metotrexato)

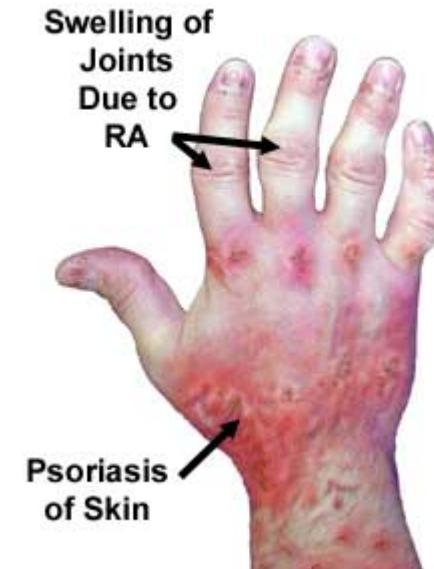
Utilizzo di Golimumab 50/100 mg per 2 anni in pazienti con PsA ha dimostrato una importante efficacia clinica e radiografica

L'aumento della dose dà solo vantaggi limitati

Sicurezza simile agli altri anti-TNF- α

Kavanaugh A et al. Ann Rheum Dis. 2012

Boyce EG et al. Clin Ther. 2010;32(10):1681-703





CERTOLIZUMAB PEGOL

Fab'



PEG

PEGylated
Fab' Fragment
40 kDa PEG

- Ultimo anti-TNF approvato per PsA
- Efficace anche in Pso
- No Fc region
 - May avoid potential Fc-mediated effects such as CDC or ADCC*
 - No recycling by FcRn which may lead to longer residency in inflamed tissue
 - Non-clinical studies suggest low or negligible level of placental transfer of a homologue Fab-fragment of certolizumab pegol

* Unico anticorpo monoclonale approvato in gravidanza e allattamento

Approved for: RA, Spon, PsA

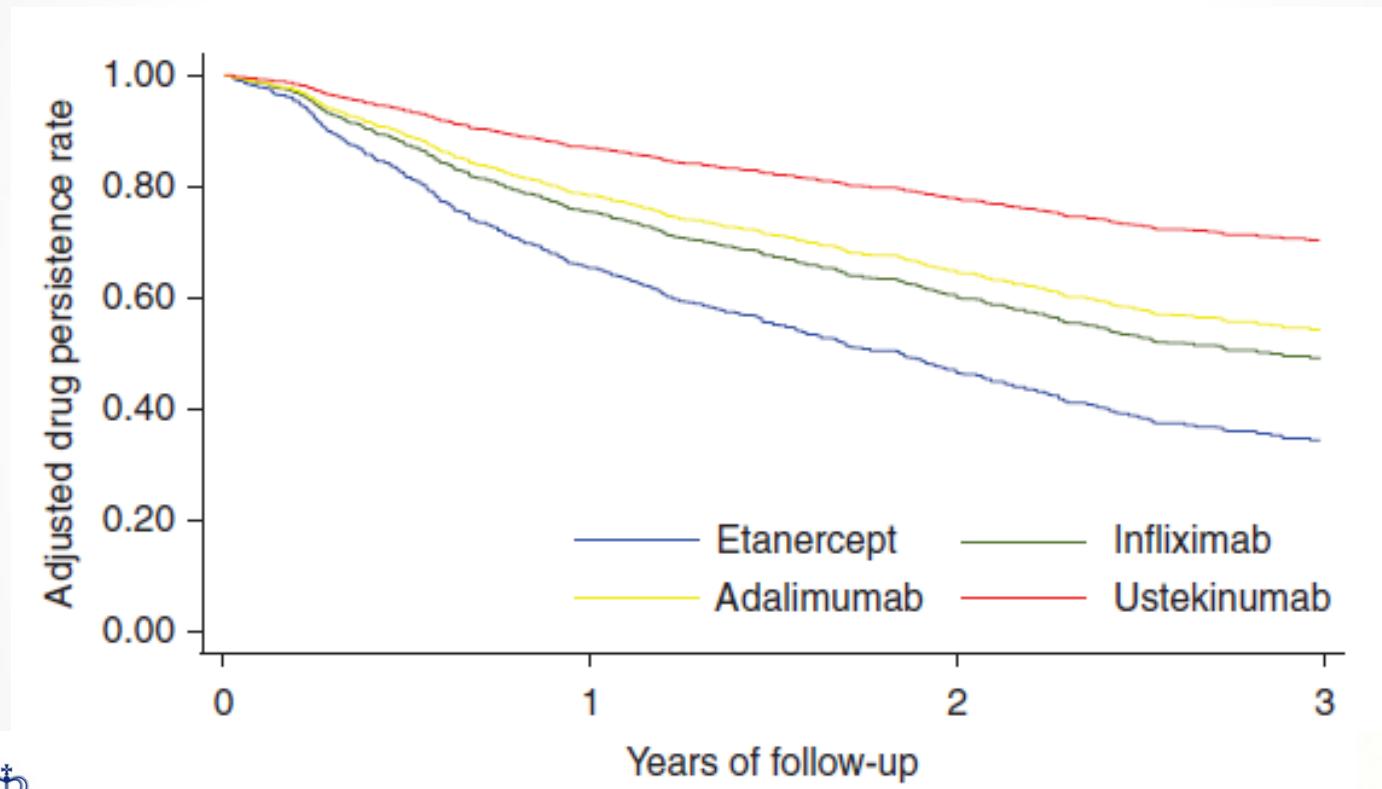
CDC= complement-dependent cytotoxicity

ADCC=antibody-dependent cell-mediated cytotoxicity

Veronese et al. *Biodrugs*. 2008;22:315-329
Chapman. *Adv Drug Deliv Rev*. 2002;54:531-545
Chapman et al. *Nature Biotech*. 1999;17:780-783
Weir et al. *Therapy*. 2006;3:535-545
UCB. CIMZIA Summary of Product Characteristics. 2012

Durata Anti-TNF- α in Psoriasis

BADBIR: 3523

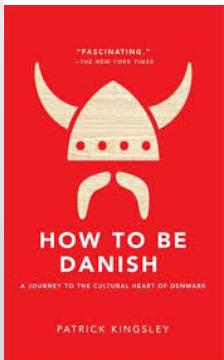
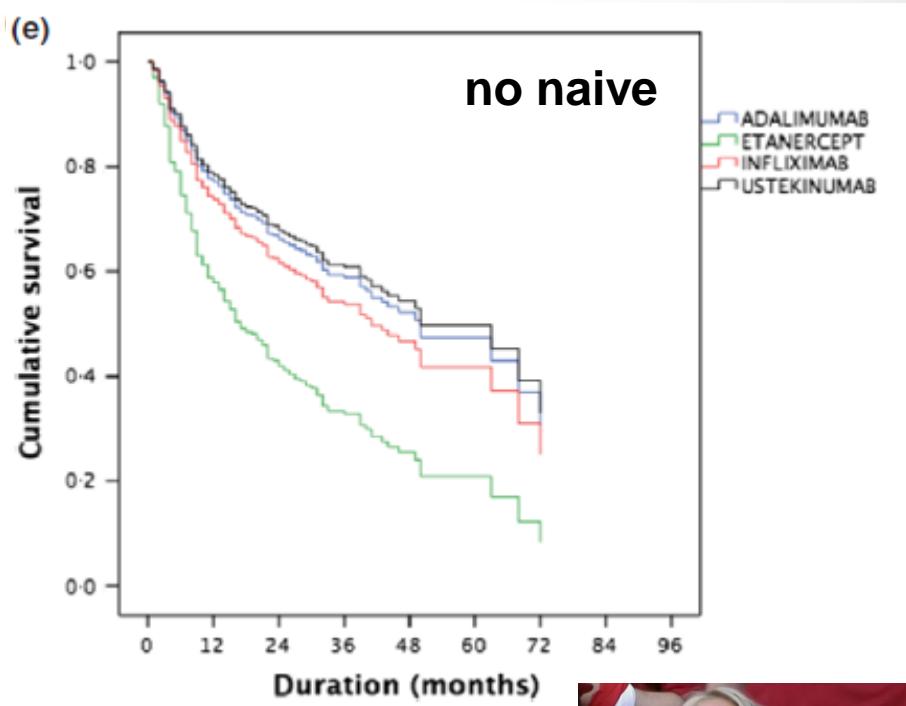
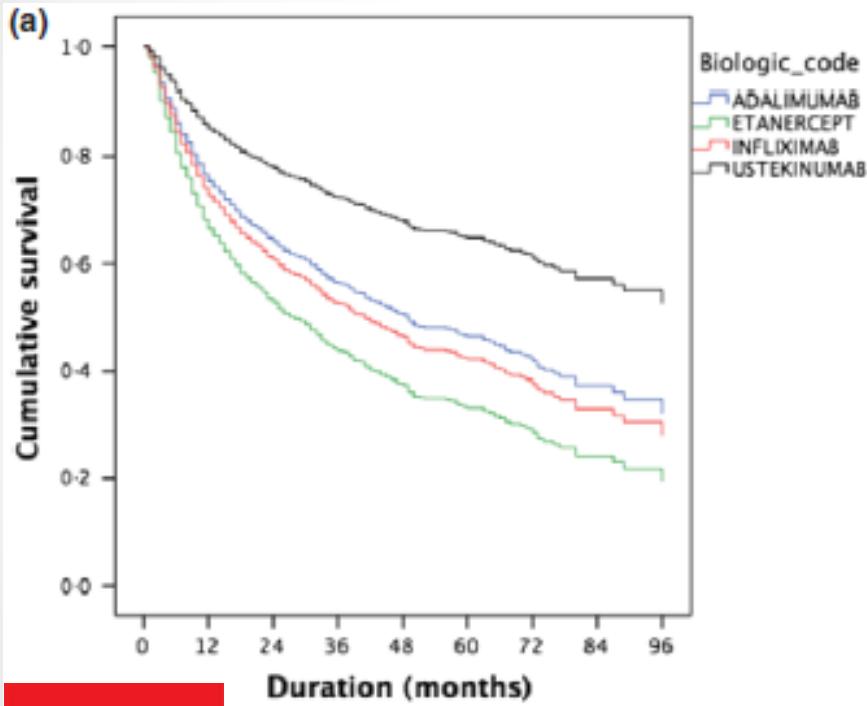


Warren RB et al. J Invest Dermatol. 2015. advance online publication



Durata Anti-TNF- α in Psoriasis

DERMBIO: 1277

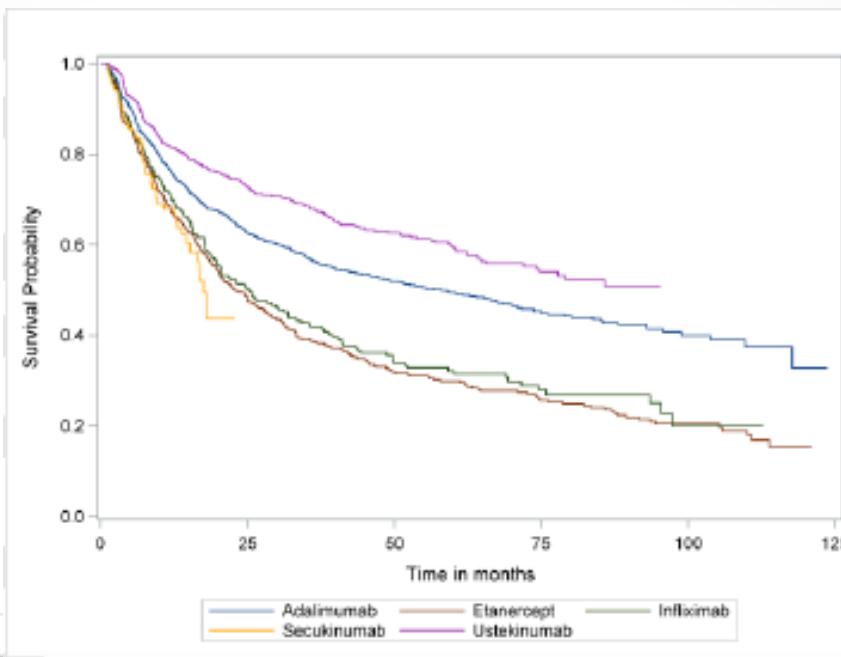


Gniadecki R et al. Br J Dermatol. 2015; 175: 244-252

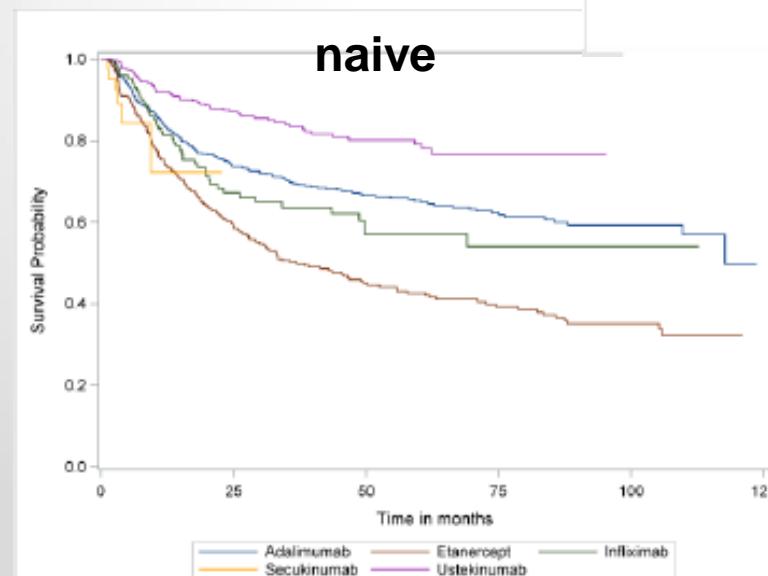


Durata Anti-TNF- α in Psoriasis

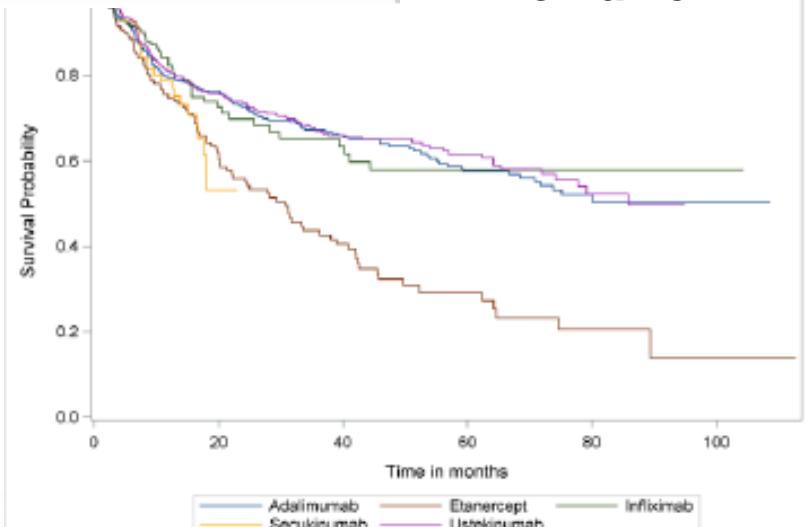
DERMBIO: 2161



naive



no naive



Durata Anti-TNF- α in Psoriasi

Adalimumab > Infliximab > Etanercept

Inf ed Eta: Trattamenti con dosaggi + elevati, riduzione intervalli

No differenza tra originator e biosimilare

No nuovi eventi avversi nel lungo termine

Inf bassa incidenza infezioni

Anti-TNF- α Survival in Psoriasis

Risultati diversi da differenti registri

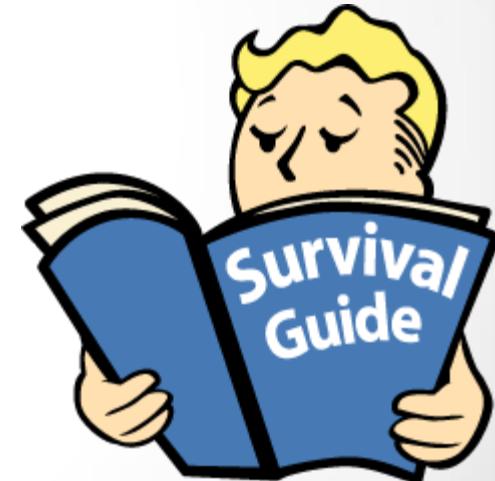
Principale causa interruzione: Perdita Efficacia

Predittori lunga durata trattamento:

- Pazienti naive
- PsA

Predittori interruzione

- Fumo
- Sesso Femminile
- Elevato DLQI al basale



Esposito M et al. Br J Dermatol. 2013; 169:666–72

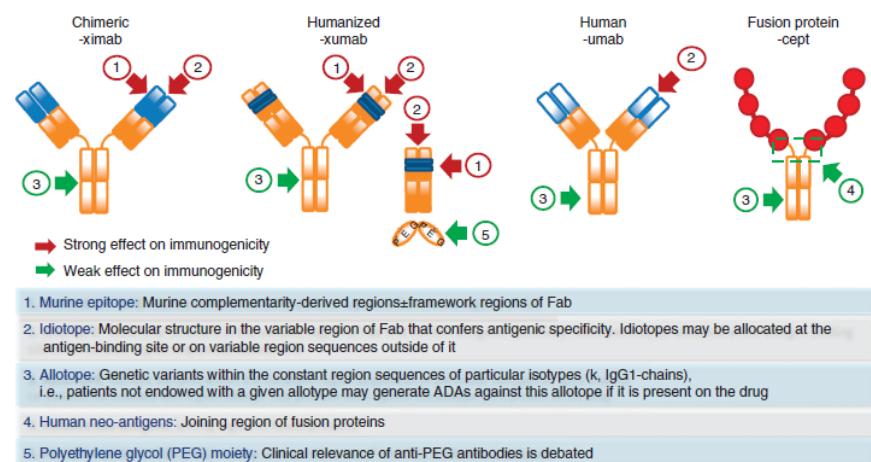
Gniadecki R et al. Br J Dermatol. 2015; 175: 244-252

Warren RB et al. J Invest Dermatol. 2015. advance online publication

Anticorpi contro Anti-TNF-α

Fattori di Rischio formazione Anticorpi:

- Struttura Molecolare
- Via Somministrazione (sc > iv)
- Paziente

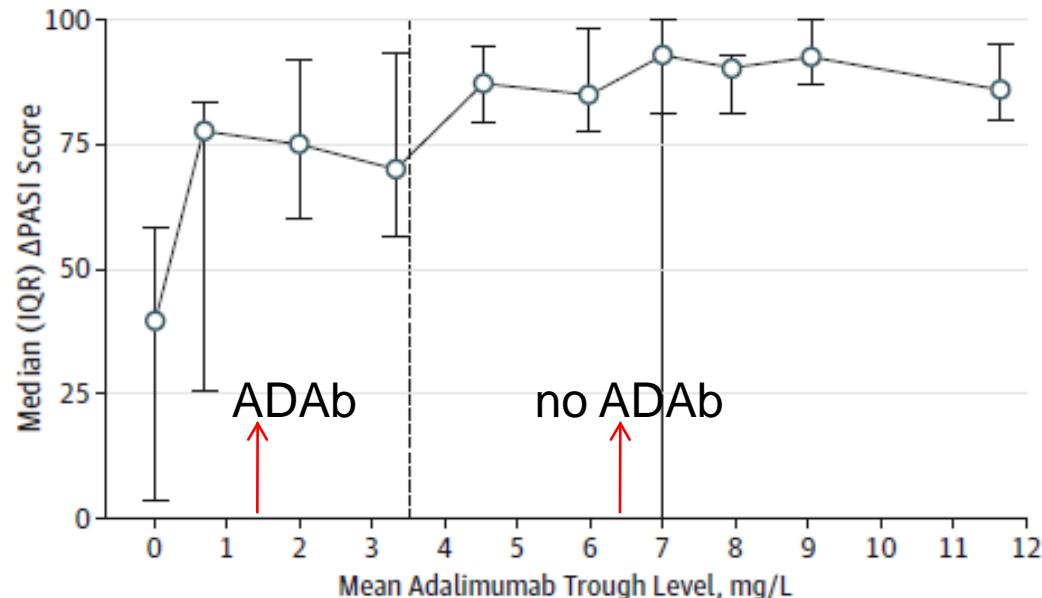
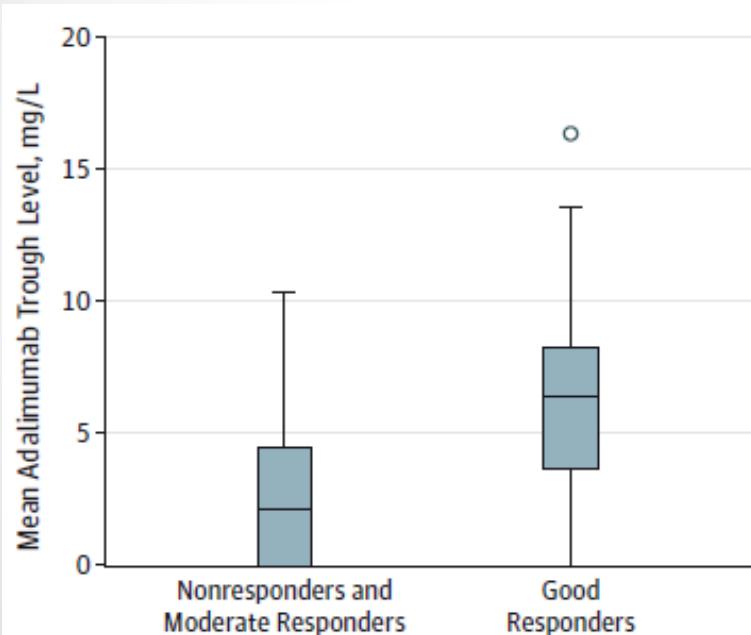


Fattori di Protezione formazione Anticorpi:

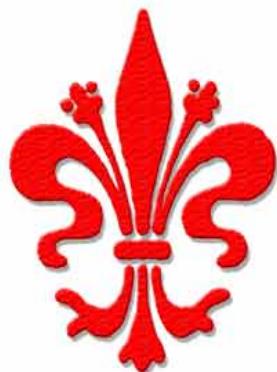
- Terapia Immunosoppressiva (Mtx)
- Alta Concentrazione farmaco

Concentrazione Sierica Terapeutica nella Psoriasi

135 pazienti trattati con Adalimumab



Italian Network for Monitoring the Imune Response to BAgents: towards Prevention and Care :



MIRBA

Coordinator: prof. E. Maggi
University of Florence
e.maggi@dmi.unifi.it



Università degli Studi di Firenze

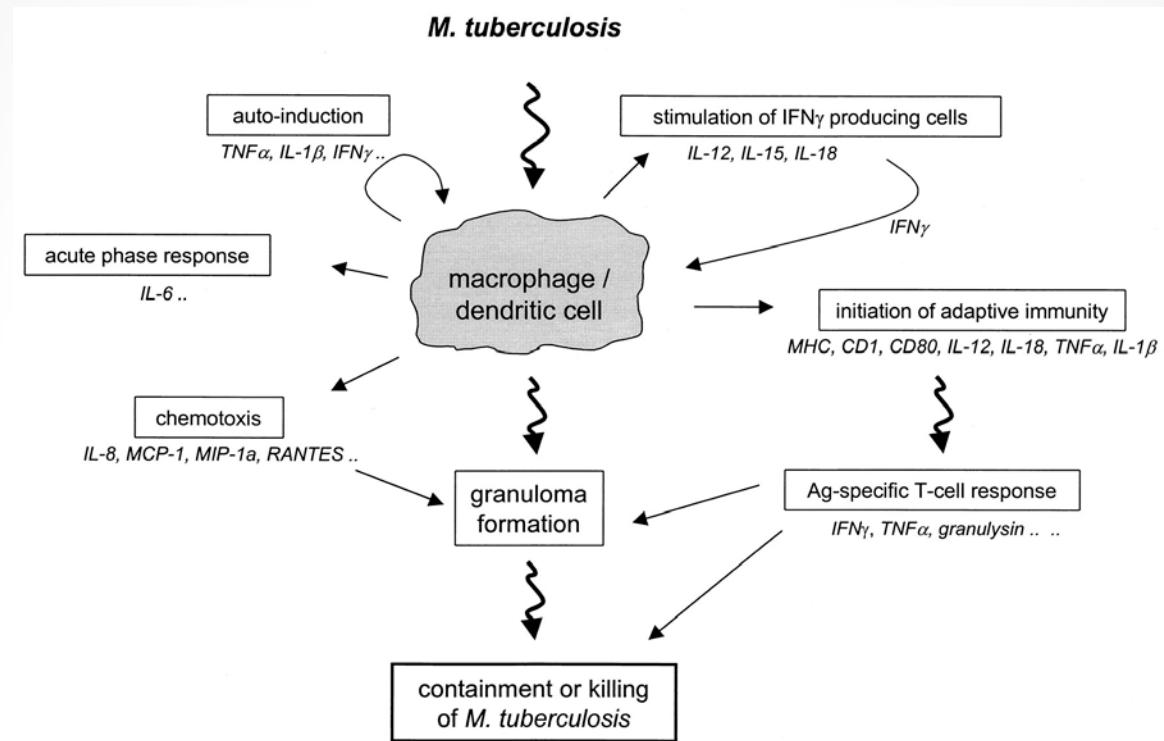
Anti-TNF- α : Effetti Collaterali

Infezioni:

- Rischio Aumentato
- Vie respiratorie e Cuta
- Herpes Zoster ?
- Riattivazione Tubercolosi



Biologici e Rischio Riattivazione TB



RISCHIO ELEVATO

ANTI-TNF- α
(Infliximab >> Adalimumab > Etanercept)

Abatacept
Tocilizumab

RISCHIO INCERTO

Ustekinumab

Pescitelli L, Ricceri F, Prignano F. J Rheumatol. 2014; 91:s65-70

Cantini F, Niccoli L, Goletti D. J Rheumatol. 2014; 91:s56-64

RISCHIO BASSO

Anakinra
Rituximab

Anti-TNF- α : Effetti Collaterali

Tumori:

Linfomi:

- Artrite Reumatide
- MICI (Linfoma T Epatosplenico)

Ramiro S et al. Ann Rheum Dis 2014;73:529-535

NMSC:

- Psoriasis

Melanoma:

- Psoriasis ?

Anti-TNF- α : Effetti Collaterali

Altro:

- Reazioni Lupus Like
- Sclerosi Multipla
- Alopecia Areata
- Psoriasi

Psoriasis da Anti-TNF-α

≈ 5% pazienti trattati (aumenta con durata trattamento)

Morbo di Crohn ≥ Artrite Reumatoide > Spondilite Anchilosante

F>M

Fumo

Psoriasis Pustolosa, Psoriasis Volgare

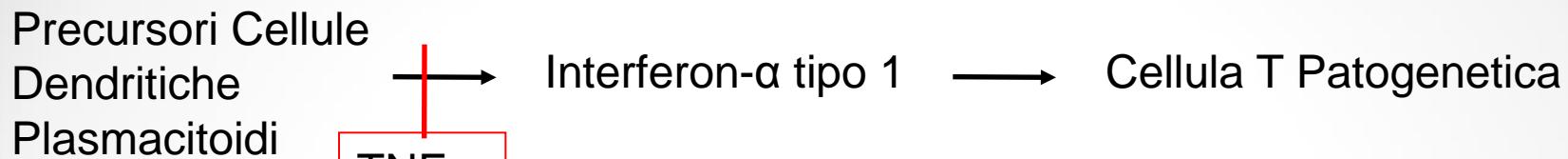
Adalimumab ≥ Infliximab >>> Etanercept

Tillack C et al. Gut. 2014; 63: 567–577

Pugliese D et al. Aliment Pharmacol Ther. 2015; 42: 880–888



Psoriasi da Anti-TNF- α



< 5%

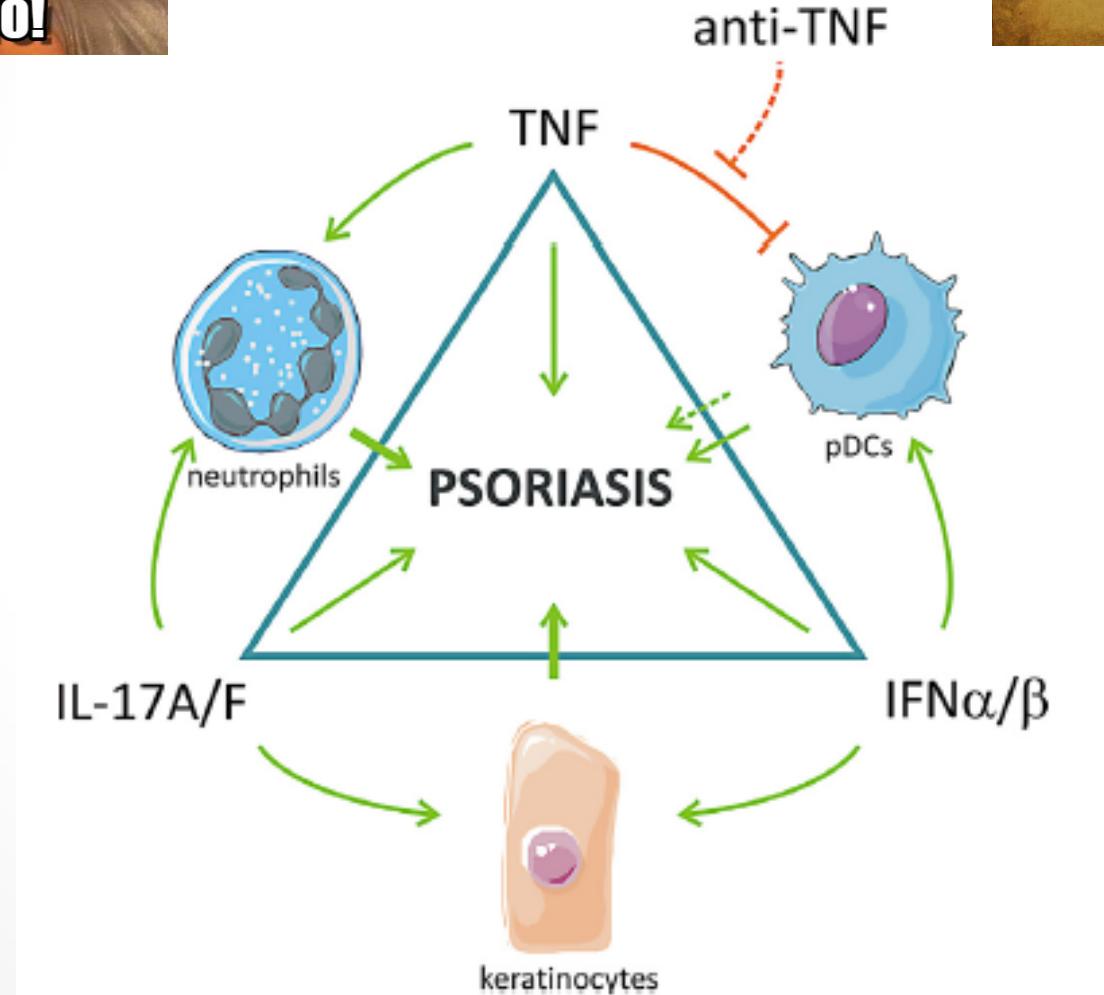
- Terapie Topiche, Fototerapia.
- Mtx

> 5%

- Terapie Topiche, Fototerapia
- Mtx, Ciclosporina, Acitretina
- Sospensione biologico



IL TRIANGOLO NO... Il Triangolo della Psoriasi



Anti-TNF- α all'Orizzonte

Drug	Mechanism of action	Company	Class
Cimzia® (certolizumab pegol)	Antibody fragment targeting TNF- α	UCB	Biologic
Valpha	Chimeric fusion protein, inhibits TNF- α and VEGF	Not commercialized*	Biologic
ESBA-105 (DLX-105)	Topical TNF- α inhibitor, antibody fragment	ESBATech, Delenex Therapeutics	Biologic
SSS-07 (APX001)	TNF- α monoclonal antibody	3SBio, Apexigen, Inc.	Biologic
AST-005	Topical TNF- α inhibitor	Aurasense Therapeutics	Biologic
XPro-1595 (XPEN 1595)	Dominant-negative biologic, inhibits soluble TNF- α	Xencor	Biologic
Protalix 106 (PRX 106)	Fusion protein targeting TNF- α	Protalix Biotherapeutics	Biologic
DLX-2751	Topical TNF- α inhibitor	Delenex	Biologic
COVA-322	TNF- α /IL-17 antibody fusion protein	Covagen	Biologic
ABT-122	Dual variable domain immunoglobulin targeting TNF- α and IL-17	AbbVie	Biologic
GSK2800528	TNF- α monoclonal antibody	GlaxoSmithKline	Biologic
TNF receptor-hyFc fusion protein	TNF receptor-hyFc fusion protein	Genexine	Biologic
SPD 304	Induces disassembly of TNF- α homotrimer	Cayman chemical	Small molecule
M21	Induces disassembly of TNF- α homotrimer	Not commercialized*	Small molecule
BIHC	Inhibits TNF- α signaling	Not commercialized*	Small molecule
C87	Binds to TNF- α	Not commercialized*	Small molecule
Qbeta-C-TNF ₄₋₂₃	Vaccine targeting TNF- α	Not commercialized*	Small molecule
Leo 32371	Decreases TNF- α , INF- γ , and IL-5	LEO Pharma	Small molecule
Curcumin	Inhibits TNF- α activity	Multiple	Naturally occurring small molecule
Elimune capsules	Inhibits TNF- α activity	Elorac, Inc.	Naturally occurring small molecule
Narigenin	Inhibits TNF- α activity	Not commercialized*	Naturally occurring small molecule

Conclusioni: Anti-TNF- α nella Psoriasi

- Efficaci nel trattamento di Pso e PsA
- 10 anni di utilizzo
- Possibili effetti collaterali
- Reazioni paradosse
- Implementazione

Grazie per l'Attenzione



24TH WORLD CONGRESS
OF DERMATOLOGY
MILAN 2019



A new ERA for a global Dermatology

SAVE THE DATE
10 - 15 JUNE, 2019
MILAN ITALY



International League
of Dermatological Societies
Skin Health for the World