

Medicina off label

Il farmaco “sbagliato”

carlomaurizio montecucco

*Unità Operativa di Reumatologia
Fondazione IRCCS Policlinico S. Matteo
Università di Pavia*

Medicina off label

Il farmaco "imputato"

- . Uso improprio
- . Uso potenzialmente pericoloso
- . Costo ingiustificato

Medicina off label

Perché mai il medico dovrebbe prescrivere un farmaco off label ?

- ✓ Malvagità
- ✓ Interesse
- ✓ Sperimentalismo
- ✓ Protagonismo
- ✓ Inconsapevolezza
- ✓ Coraggio
- ✓ Deontologia

Medicina off label e Medicina difensiva

Quando il medico dovrebbe prescrivere un farmaco off label ?

- ✓ **Mai**

- ✓ **Assoluta necessità di trattamento e sufficiente evidenza di efficacia e tollerabilità in caso di**
 - ✓ Inefficacia delle alternative terapeutiche approvate
 - ✓ Intolleranza o controindicazione alle alternative terapeutiche
 - ✓ Mancanza di alternative terapeutiche approvate (previo consenso informato)

Medicina off label e malattie rare

- ✓ Malattia rara = casistica insufficiente per RCTs
- ✓ Malattia rara = tutti i trattamenti sono off label



Medicina off label

Il farmaco "imputato"

- . Uso improprio
- . Uso potenzialmente pericoloso
- . Costo ingiustificato

Medicina off label

Il farmaco "imputato"

- ✓ cortisone
- ✓ colchicina (FMF, vasculiti)
- ✓ aspirina (gravidanza aPL)
- ✓ HD IgIV (miositi)
- ✓ anti-TNF (uveiti, vasculiti)

TNFa blocker indications

	Infliximab	Etanercept	Adalimumab
RA	+	+	+
AS	+	+	+
PsA	+	+	+
Psoriasis	+	+	+
Crohn's	+		+
UC	+		+
JIA		+	

Anecdotal studies of TNFa blockers

(Furst DE et al. Ann Rheum Dis 2008)

Disease	Author(s)	Medication	No. of patients
Adult Still's disease	Huffstutter and Sienknecht ²⁴⁷	Infliximab	2
	Kraetsch et al ²⁴⁸	Infliximab	6
	Weinblatt et al ⁴⁹	Etanercept	12
	Fernandez-Nibro ²⁴⁹	Etanercept	3
Behçet's disease	Estrach et al ²⁶⁰	Infliximab/ adalimumab	7
	Gulli et al ²⁶¹	Infliximab	1
	Hassard et al ²⁶²	Infliximab	1
	Licata et al ²⁶³	Infliximab	1
	Melikoghu et al ²⁶⁴	Etanercept	20
	Morillas et al ²⁶⁵	Adalimumab/ etanercept	
	Rosenbaum et al ²⁶⁶	Anti-TNF	1
	Saulsbury and Mann ²⁶⁷	Infliximab	1
	Sangle et al ²⁶⁸	Infliximab	1
	Sfikakis et al ²⁶⁹	Infliximab	5
	Sfikakis ²⁷⁰	Infliximab	11
	Ribi et al ²⁷¹	Infliximab	1
	Sweiss et al ²⁷²	Infliximab	3
Van Laar et al ²⁷³	Adalimumab	6	
Dermatomyositis	Hengstman et al ²⁸²	Infliximab	2
	Miller et al ²⁸³	Etanercept	10
	Sprott et al ²⁸⁴	Etanercept	1
	Nzeusseu et al ²⁸⁵	Infliximab	1
	Saadeyh ²⁸⁶	Etanercept	4
	Norman et al ²⁸⁷	Etanercept	2

Adult Still's disease

Behçet's disease

Dermatomyositis

Anecdotal studies of TNFa blockers

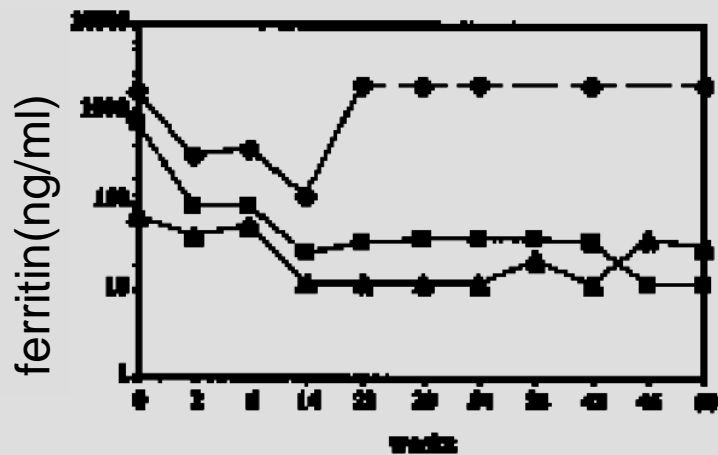
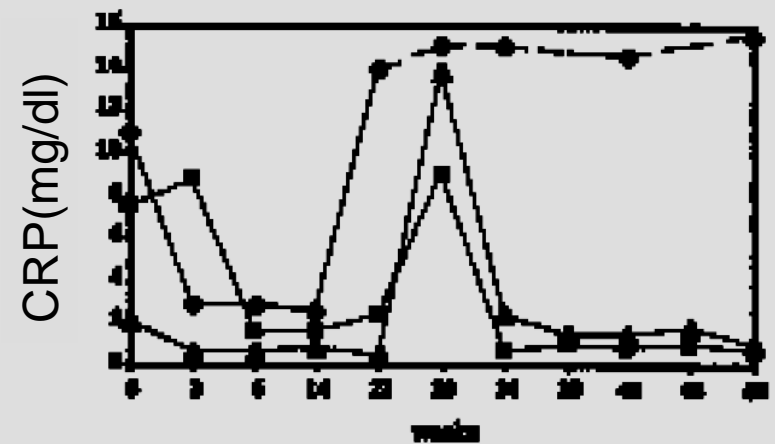
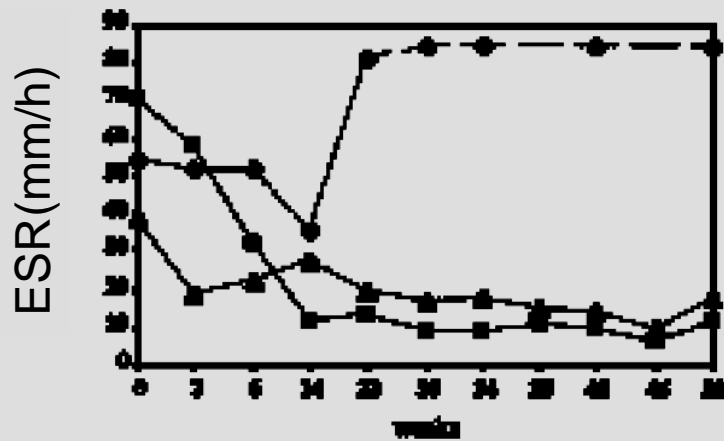
(Furst DE et al. Ann Rheum Dis 2008)

Disease	Author(s)	Medication	No. of patients	
Uveitis	Estrach et al ²⁶⁰	Infliximab/ adalimumab	7	
	Joseph et al ²⁶⁹	Infliximab	5	
	Smith et al ²⁷⁰	Etanercept	7	
	Braun et al ²⁷¹	Etanercept/Infliximab	717 (uveitis in AS)	
	Foster et al ²⁷²	Etanercept	20 (ineffective)	
	Biester et al ²⁷³	Adalimumab	18	
	Foeldvari et al ²⁷⁴	Anti-TNF	47	
	Vazquez-Cobain et al ²⁷⁵	Adalimumab	14	
	Reiff et al ²⁷⁶	Etanercept	10	
	Schmeling and Horneff ²⁷⁷	Etanercept	20 (ineffective)	
	Guignard et al ²⁷⁸	Adalimumab	8	
	Vasculitis (see also Behcet's, GCA, Takayasu's, Wegener's)	Booth et al ²⁷⁹	Infliximab	32
		Feinstein and Arroyo ²⁸⁰	Etanercept	1
Van dan Bijl ²⁸¹		Infliximab	11	
Saji et al ²⁸²		Infliximab	1 (Kawasaki's)	
Sangle et al ²⁶⁸		Infliximab	1 (Churg-Syrauss)	
Wegener's granulomatosis	Arbach et al ²⁸³	Etanercept/infliximab	3	
	Gause et al ²⁸⁴	Infliximab	10	
	Sangle et al ²⁶⁸	Infliximab	3	

**Uveitis
&
Vasculitis**

Infliximab in the treatment of adult Still's disease refractory to conventional therapy

Cavagna L, Caporali R, Epis O, Bobbio-Pallavicini F, Montecucco C.



Clin Exp Rheumatol. 2001

Tumour necrosis factor α blocking agents in refractory adult Still's disease: an observational study of 20 cases

B Fautrel, J Sibilila, X Mariette, B Combe, the Club Rhumatismes et Inflammation

Ann Rheum Dis 2005;64:262-266. doi: 10.1136/ard.2004.024026

Table 1 Summary of patient characteristics

Characteristic	
Age at ASD diagnosis	
Mean (SD) (range)	32.2 (19) (11 to 72)
Median	28
Childhood onset (no.)	4
Disease free interval between childhood and adult symptoms	1
Disease duration (years)	
Mean (SD) (range)	8.5 (6) (2 to 21)
Median	6.5
Age at anti-TNF start (years)	
Mean (SD) (range)	40.7 (17) (18 to 74)
Median	34.5
Predominant clinical expression	
Chronic arthritis	15
Systemic	5
Symptoms (no.)	
Fever	20
Arthralgia	20
Polyarthritis	18
Sore throat/pharyngitis	14
Rash	16
Seritis	4
Lymphadenopathy	6
Increased leukocyte level	20
Polymorphonuclear level >10 000 mm ³	20
Abnormal liver function test result	6
High serum ferritin level	14
Disseminated intravascular coagulation syndrome	5
Previous treatments	
Prednisone	20
Methotrexate	20
Intravenous polyvalent immunoglobulin	5
Sulfasalazine	2
Hydroxychloroquine	6
Gold salts	2
D-Penicillamin	1
Thalidomide	1
Cyclosporine A	5
Cyclophosphamide	4
Azathioprine	3

Table 3 Treatment response

	All treatments (n=25)*	Etanercept (n=10)	Infliximab (n=15)
Treatment duration (months)			
Mean (SD)	13 (14)	13 (14)	14 (14)
Median	9	9	10
Range	1 to 44	1 to 43	1 to 44
Response to therapy			
Complete remission	5	1	4
Partial response	16	7	9
Failure	4	2	2

*A total of 25 treatments in 20 patients were analysable. 10 patients received etanercept, 15 infliximab, and 5 both drugs.

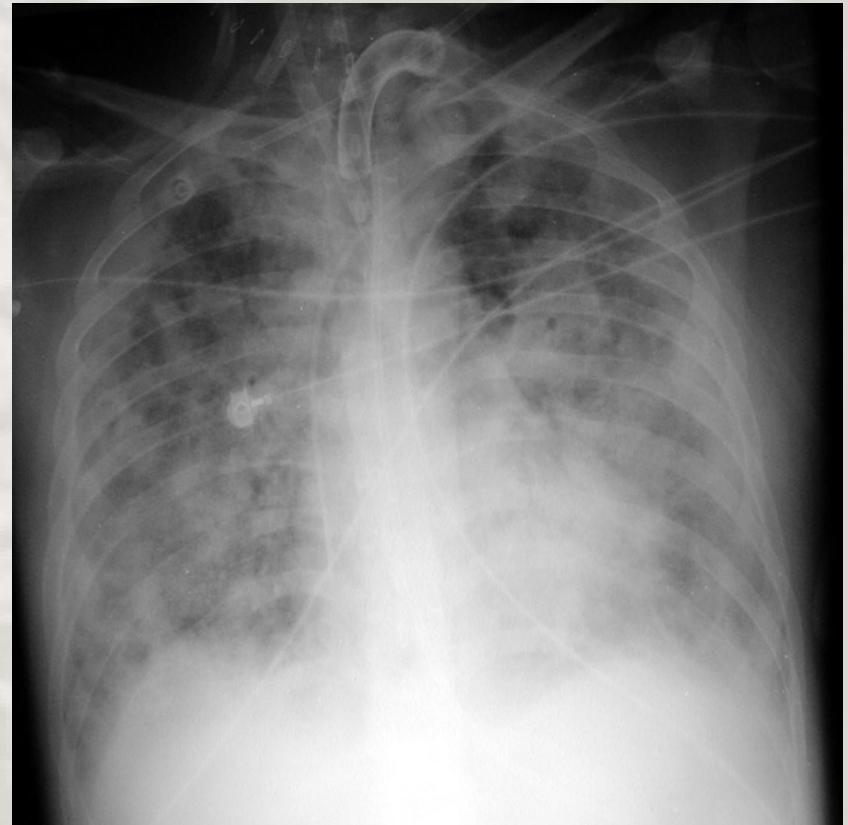
Acute respiratory distress syndrome in adult-onset Still's disease is often fatal

- Manganelli P et al *Clin Exp Rheumatol* 2003
- Mito K. *Nihon Kokyuki Gakkai Zasshi* 2002
- Suleiman M et al *Scand J Rheumatol* 2001
- Iglesias J et al *Chest* 1999
- Pedersen JE et al *Intensive Care Med* 1991

Acute respiratory distress syndrome in adult-onset Still's disease:

**Successful treatment
with repeated Infliximab
infusions in a 41 years
old woman**

Broggini M, Montecucco C (unpublished)



Anti-TNF α in PAN

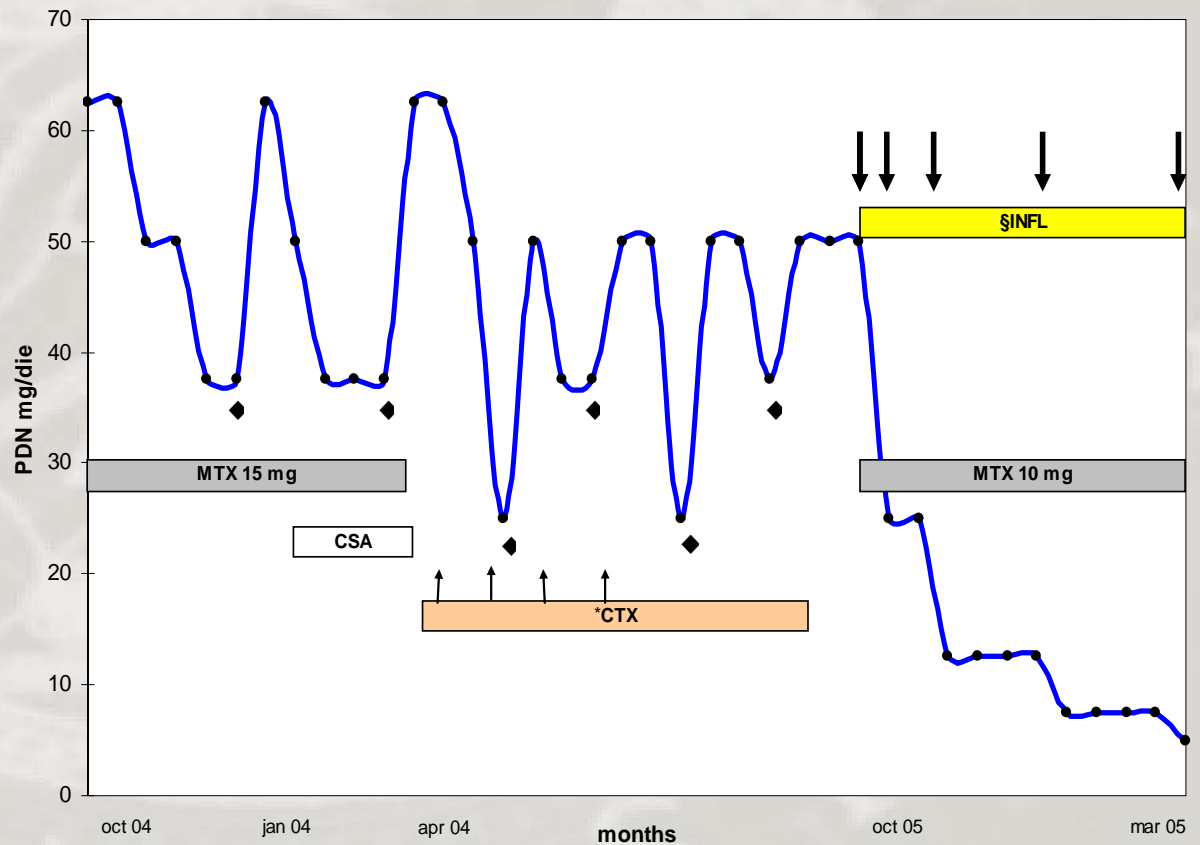
- Vega Gutierrez J et al. Successful treatment of childhood cutaneous polyarteritis nodosa with infliximab. *J Eur Acad Dermatol Venereol* 2007;21(4):570-1
- Brik R et al. Tumor necrosis factor blockade in the management of children with orphan diseases. *Clin Rheumatol* 2007;26(10):1783-5.
- Wu K et al. A new treatment for polyarteritis nodosa. *Nephrol Dial Transplant* 2006;21(6):1710-2
- de Kort SW et. Infliximab in a child with therapy-resistant systemic vasculitis. *Clin Rheumatol* 2006;25(5):769-71.
- Al-Bishri J et al. Refractory polyarteritis nodosa successfully treated with infliximab. *J Rheumatol* 2005;32(7):1371-3

Case report

Male, 40 years

PAN onset:
Oct 2003

Previous therapy:
high-dose steroids





Medicina off label

Il farmaco sbagliato ?

Il farmaco indovinato ?



Corsi residenziali
gratuiti per
specializzandi in
Reumatologia

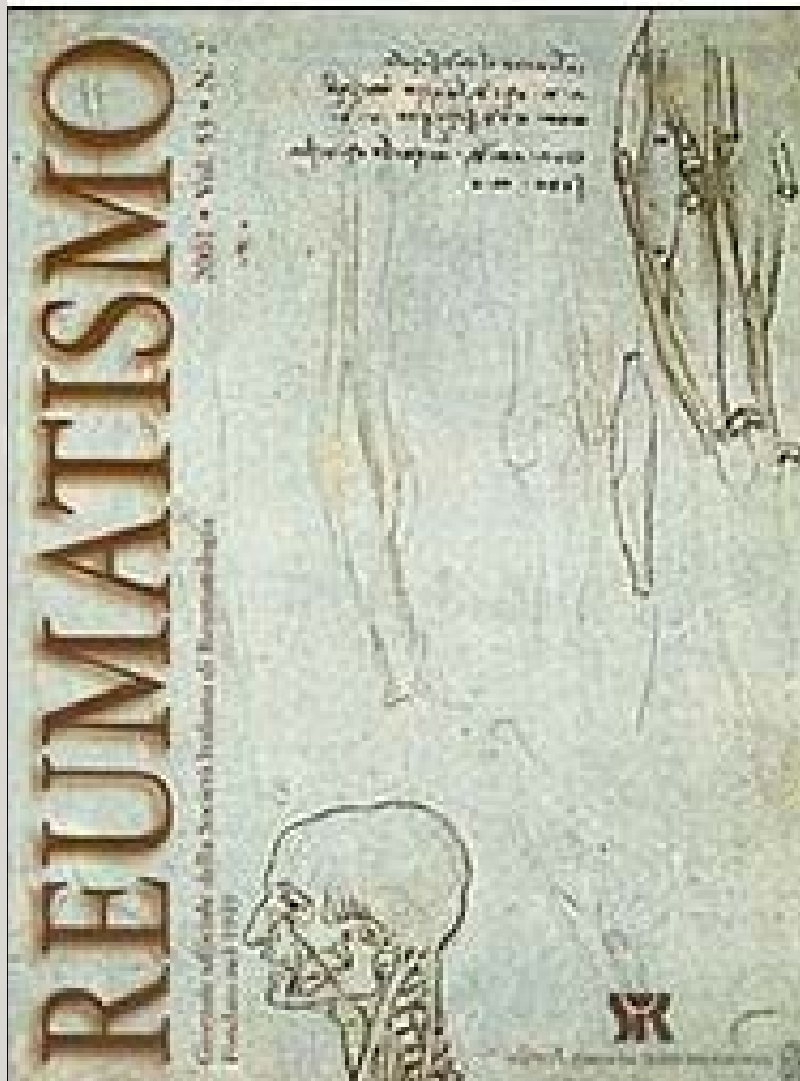
I anno: diagnostica per immagini in Reumatologia

II anno: analisi del liquido sinoviale

III anno: le misure in reumatologia – laboratorio e clinimetria

IV anno: le malattie rare in Reumatologia

Medicina off label



**Numero monografico:
Raccolta della letteratura sui
trattamenti off label nelle malattie
reumatologiche.**

**Prima edizione 2007
Aggiornamento previsto per fine
2009**

**Recepito dalla Regione Toscana
DGR 836/2008**

Direttiva alle aziende sanitarie toscane
sull'impiego in reumatologia dei
farmaci fuori dalle indicazioni di
registrazione.

Medicina off label

- ✓ Conoscenza
- ✓ Prudenza
- ✓ Condivisione

Per non sbagliare farmaco