Anti-TNFalfa e reazioni da ipersensibilità

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Pichler WJ (ed): Drug Hypersensitivity. Basel, Karger, 2007, pp 160–174

Adverse Side Effects to Biological Agents

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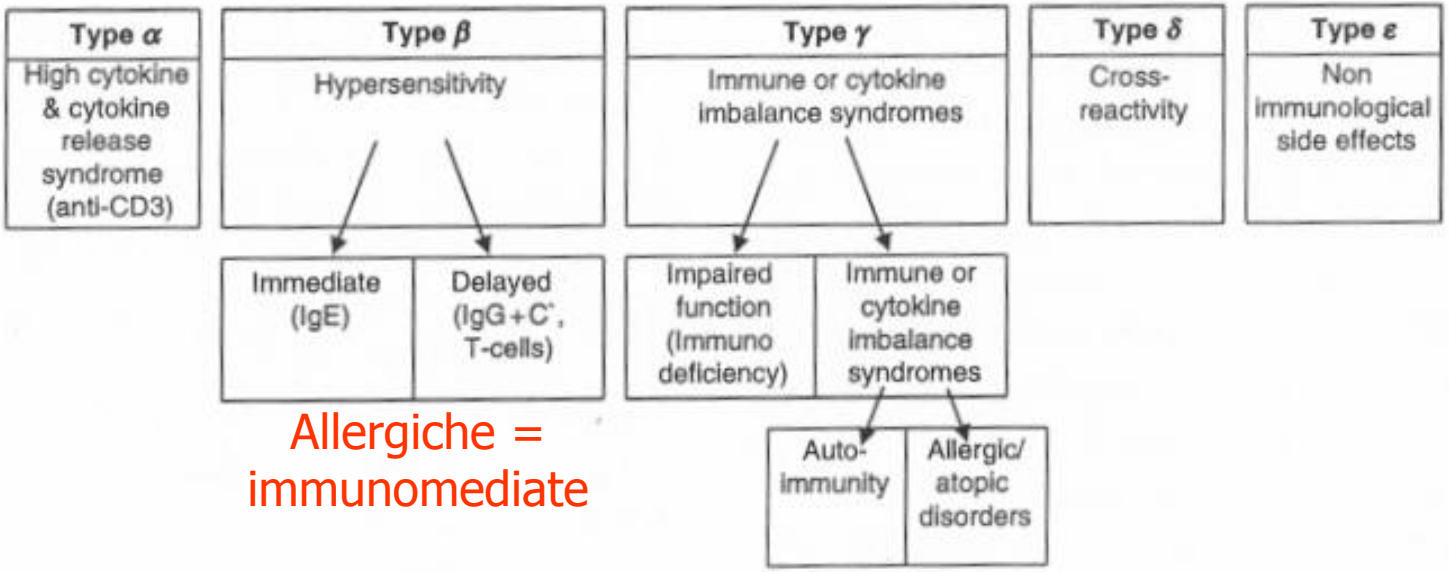
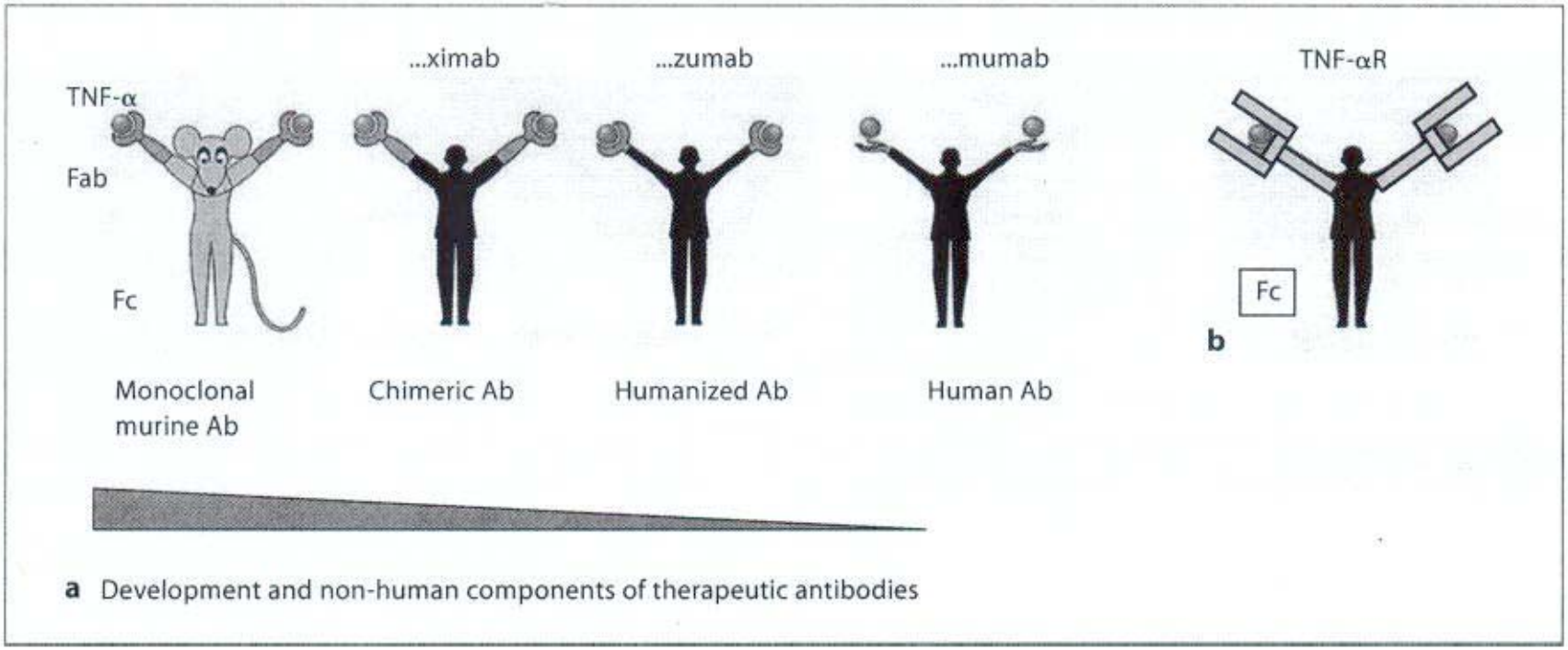
Pichler WJ, Allergy 2006;61:912-920

Non allergiche



Allergiche = immunomediate

Type of adverse effects of biological agents.



a Development and non-human components of therapeutic antibodies

Hypersensitivity reactions to TNF alpha antagonists

Infliximab

- A chimeric IgG1 anti-TNF alpha antibody containing the antigen-binding region of the mouse antibody and the constant region of the human antibody. The murine portion, comprising 25% of the antibody, is antigenic. It has a MW of 149 kDa.
- Approved fot therapy of rheumatoid arthritis, psoriatic arthritis, Crohn's disease, ankylosing spondylitis, plaque psoriasis and ulcerative colitis

Reazioni allergiche a farmaci

- Tipo I o IgE-mediate o immediate (entro 1 ora): orticaria, angioedema, shock, broncospasmo (tosse secca, fischio espiratorio, costrizione toracica)
- Tipo IV o cellulo-mediate o ritardate (dopo 1 ora): rash morbilliformi o maculo-papulari, eritema multiforme, Stevens-Johnson, Lyell, AGEP, DRESS, ecc

Hypersensitivity reactions to TNF alpha antagonists

Acute Infusion Reactions to infliximab:

- they occur **within 24 hours** after i.v. administration, usually between 10 minutes and 4 hours, with symptoms like **hypotension/hypertension, chest pain, dyspnea, laringospasm, fever, urticaria, angioedema**
- most of acute IR are mild or moderate and do not necessitate a suspension of the treatment but only a **reduction in the rate of infusion or a premedication** (Cheifetz 2005, Lequerré 2006). Actually, many authors consider acute IR similar to the **"red man syndrome"** typical of vancomycin (Lobel 2003) or "niacin-like reactions" described for vitamin PP (Becker 2004).
- **severe** acute IR must be managed more carefully, because are more prone to recidivate in case of readministration. In these cases a **desensitization** protocol may be indicated (Puchner 2001, Lelong 2005, Duburque 2006); an **"induction of tolerance"** is a more appropriate definition, because the procedure has to be repeated at each administration as they are scattered in the time.

Hypersensitivity reactions to TNF alpha antagonists

Delayed Infusion Reactions to infliximab:

- delayed: from 24 hours to 14 days after administration usually after 5-7 days, with symptoms like arthralgias, fever, malaise, urticarial rash, myalgias, angioedema, lymphoadenopathy, itching (serum sickness?).
- the prognosis is usually excellent with a lack of any serious long term sequelae. Potentially life-threatening serum sickness reactions should be a contraindication to further infliximab treatment, even if uneventful retreatment cases have been described, in association to an immunosuppressive therapy and premedication (Kugathasan 2002, Sandborn 2002). In any case, in these patients high titers of antibodies to infliximab are present and, as a consequence, a reduced efficacy of the treatment is likely.

Acute and delayed infusion reactions (IR) to infliximab

Disease	No pts	IR acute	IR delayed	Reference
RA,PA	49	12%		Vultaggio 2008
RA	152	23%		Figuereido 2008
IBD	23	35%		Kohlo 2007
IBD	243	16.5%		Jabostein 2005
RA	355	13.5%	0%	Sany 2005
RA,SPA	289	19%		Kapetanovic 2006
RA,SPA	203	11.3%	2.4%	Lequerré 2006
CD	19	15.7%	0%	Hyams 2000
CD	125	27%		Baert 2003
CD	40		25%	Hanauer 1999
CD	53	13.2%		Farrell 2003
IBD	34	23.5%		Miele 2004
RA	51	5.8%		Wolbinck 2006
CD	165	9.7%	1.8%	Cheifetz 2003
CD,RA	771	17%		Schaible 2000
All	2088	16%		All

Acute infusion reactions to infliximab: skin tests and induction of tolerance (IOT)

Dis	No pts	Skin tests	I.O.T.	Drug tolerated afterw.	Ref
CD	1	ND	Success		Puchner 2001
CD	1	Scratch neg	Unsuccess	Etanercept	O'Connor 2002
CD	3	ND	ND	Infliximab (2/3)	Hyams 2000
CD	1	ND	ND		Soykan 2000
CD	2	ND	ND		Diamanti 2002
CD	3	ND	ND	Infliximab (slow)	Lobel 2003
CD	1	ND	ND	Adalimumab	Youdim 2004
CD	4	I.d. neg	Success		Lelong 2005
Still	1	I.d. pos (control?)	ND		Domm 2003
PA	1	ND	ND		Chavez 2005
RA	6	Prick neg			Vultaggio 2008

Hypersensitivity reactions to TNF alpha antagonists: case reports

Infliximab acute infusion reactions

- Patient C.F: male, 50-year old, in therapy since 2 years for ankylosing spondylitis. After 10' from the beginning of the infusion he experienced cough, dyspnea (sensation of throat swelling), sweating, warm face, for 10'. Prick and intradermal test negative. Switched to etanercept, without reactions.
- Patient M.I: female, 65-year ald, with rheumatoid arthritis. At the third dose she experienced, after 30': sweating, hypotension and labial cyanosis, for two hours. Tryptase was normal. Total IgE before reaction and one month later was unchanged and in the normal range. Prick and intradermal test were negative. Switched to etanercept without reactions.

Hypersensitivity reactions to TNF alpha antagonists: case reports

Infliximab acute infusion reactions

- We had 4 reactions out of 27 patients treated (14.8%)
- Prick and intradermal tests were negative
- Non allergic hypersensitivity reactions

Hypersensitivity reactions to TNF alpha antagonists

Adalimumab

- A recombinant fully human high affinity IgG1 monoclonal antibody against TNF alpha; it was created using phage display technology with human derived heavy and light chain variable regions and human IgG:k constant regions. It has a MW of 148 kDa.
- Approved for therapy of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and Crohn's disease

Hypersensitivity reactions to TNF alpha antagonists

Etanercept

- A soluble TNF-receptor fusion protein: it is composed of two dimers, each with an extracellular, ligand-binding portion of the higher-affinity type 2 TNF receptor (p75) linked to the Fc portion of human IgG1. It has a MW of 150 kDa.
- Approved for use in the treatment of rheumatoid arthritis, ankylosing spondylitis, juvenile rheumatoid arthritis, psoriasis, and psoriatic arthritis.

Hypersensitivity reactions to TNF alpha antagonists

Injection Site Reactions to etanercept and adalimumab

- Erythema, edema and itching in the site of the subcutaneous administration, appearing within 24-48 hours, peaking at 48 hours and lasting 3-5 days. Most of ISR resolve without treatment or with topical antihistamine or corticosteroid cream. Usually they occur in the first-second month of therapy and fade over time.
- There are only 2 allergological studies in the literature

Injection Site Reactions (ISR) to etanercept and adalimumab (s.c.)

Disease	Etanercept ISR (No/total)	Adalimumab ISR (No/total)	Reference
RA,PA,PS,IBD	20% (21/103)		Zeltser 2001
	42% (25/59)		Weinblatt 1999
	45% (70/154)		Moreland 1999
	18% (67/367)		Keystone 2004
RA	29% (64/222)		Dore 2007
RA	37% (129/349)		www.enbrel.com
PA		6.6% (10/151)	Mease 2005
RA		15.3% (33/209)	Weinblatt 2003
All	30% (376/1254)	12% (43/360)	All

Hypersensitivity reactions to TNF alpha antagonists

- Paltiel et al "Immediate type I hypersensitivity response implicated in worsening injection site reactions to adalimumab" Arch Dermatol 2008;144:1190 – positive intradermal tests and leukocytes histamine release.
- Gonzalo-Garijo et al "Severe generalized exanthema due to etanercept given for severe plaque psoriasis" Ann Allergy Asthma Immunol 2008;100:612 – positive intradermal tests

Injections site reactions to TNF-alfa blocking agents with positive skin test Benucci M, Manfredi M, Demoly P, Campi P Allergy 2008;63:138-139

Table 1. Results of skin tests

	Etanercept*					Adalimumab*			
	Prick	Intradermal				Prick	Intradermal	Intradermal	Patch
Reading	20 min	15 min	15 min	15 min	24–48 h	20 min	15 min	24–48 h	24–48 h
Concentration (mg/ml)	25	5	1	0.1	5	50	5	50	50
Controls (10)	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Case 1	0/0	7/12	7/10	5/5	0/0				
Case 2	0/0	6/15	6/6	0/0	0/0				
Case 3						0/0	0/0	7/7	0/0
Case 4						0/0	0/0	7/15	0/0

*Diameter in millimeter of wheal/flare.

Hypersensitivity reactions to TNF alpha antagonists: case reports

Etanercept injection site reactions (ISR)

- Serum specific **IgE** to etanercept, assayed by means of nitrocellulose and epoxy-activated sepharose 6B as solid phases and also using Immuno CAP Phadia, especially developed in collaboration with our laboratory, was negative in both patients.
- Afterwards, both patients experienced an ISR at the first dose of adalimumab.
- Intradermal test with adalimumab was positive at immediate reading in M.A. and only at late reading (24 hours) in L.L. lasting for 5 days.

Hypersensitivity reactions to TNF alpha antagonists

Excipients:

- **Infliximab: contains sucrose and polysorbate 80.**
- **Etanercept: the lyophilized vial containing 25 mg etanercept, 40 mg mannitol, 10 mg sucrose and 1.2 mg tromethamine (trometamol = tris buffer) has been reconstituted with distilled water and the dilutions have been made in saline solution.**
- **Adalimumab: the commercial preparation contains in 0.8 mL of distilled water: 40 mg adalimumab, 9.6 mg mannitol, 0.8 mg polysorbate 80 (poly-oxy-ethilene sorbitan monooleate = Tween 80).**
- **Intradermal test with with mannitol, an excipient present in both drug, was negative.**

Recall injection-site reactions associated with etanercept therapy: report of two new cases with immunohistochemical analysis

M. A. González-López, V. M. Martínez-Taboada*, M. C. González-Velat, R. Blanco*, H. Fernández-Llaca, V. Rodríguez-Valverde* and J. F. Val-Bernalt

*Departments of Dermatology, *Rheumatology, and tPathology, Hospital Universitario Marqués de Valdecilla, Universidad de Cantabria, Santander, Spain*

Clinical and Experimental Dermatology 2007;32:672

"Our observations suggest that injection site reactions to etanercept may be mediated by classic cellular-hypersensitivity reactions by CD4+ T lymphocytes"

Anaphylactic shock to adalimumab
Campi P, Manfredi M, Valentini M, Benucci M
Eur J Dermatol 2008;18:259-260

- Female, 61 years with spondylarthritis. From the sixth dose an ISR occurred. In May 2007 intradermal tests were positive at late reading.
- Adalimumab was withhold in August till mid September. The first two doses provoked ISR; at the third dose at mid October she experienced after one hour: itching at palms and soles, angioedema of tongue and lips. At the following dose after 30' she had itching to all body, lips angioedema, dizziness, visual disturbances. She also noticed a loss of effectiveness after reassuming the drug in September. It is to notice that she stopped oral steroid from September.

Systemic hypersensitivity reactions with adalimumab (no skin tests!)

- Sànchez-Cano D et al. Urticaria and angioedema in a patient with Behçet's disease treated with adalimumab. Clin Exp Rheumatol 2006 ;24 :S128
- George SJ et al. Adalimumab-induced urticaria. Dermatol Online J 2006;12:4
- Nikas SN et al. Urticaria and angiedema-like skin reactions in a patient treated with adalimumab. Clin Rheumatol 2007;26:787
- Dalmau J et al. Acute generalized skin eruption due to adalimumab: report of two cases. J Eur Acad Dermatol Venereol 2007;21:1105
- Mallo S et al. Adalimumab-induced urticaria. Actas Dermosifiliogr 2007;98:511

Anaphylactic shock to adalimumab
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- Skin test with adalimumab in December 2007: strong positive results at the immediate reading both with prick test and intradermal test. Negative results at the late reading.
- Serum IgE specific to adalimumab was not detectable using Immuno CAP Phadia, especially developed in collaboration with our laboratory. Total IgE was 6.4 KU/l.

Anaphylactic shock to adalimumab
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Conclusions-1: we described the first case of systemic reaction to adalimumab with positive skin tests.

Features, timing and results of skin tests suggest a cell-mediated type IV immune mechanism for the ISR and an IgE-mediated type I mechanism for the two systemic reactions; however the negative in vitro test for specific **IgE** suggests that specific **IgG** might be responsible, possibly for both.

A non-IgE-mediated anaphylaxis has been described in mice involving **specific IgG**, FcγRIII, macrophages and PAF, in cases of repeated exposure to large quantities of antigen (Finkelman JACI 2005).

Anaphylactic shock to adalimumab
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Conclusions-2:

- **The allergen could be the Fc of human IgG1, present in both molecules, or the TNF alpha itself, modified as a consequence of the binding of both etanercept or adalimumab**
- **Also an hypersensitivity (allergic?) to polysorbate 80 could be responsible for the reactions (see omalizumab – Price Allergy Asthma proc 2007 and erythropoietin - Limaye JACI 2002): however, Paltiel performed in his 2 patients, skin tests with adalimumab vehicle, containing also polysorbate 80, with negative results.**

Correlation between atopy and hypersensitivity reactions during therapy with three different TNFalpha blocking agents in rheumatoid arthritis.

M.Benucci, M.Manfredi, G.Saviola, P.Baiardi, P.Campi

Clinical and Experimental Rheumatology, in press

- 90 patients
- first year of treatment
- infusion reactions to infliximab
- ISR to etanercept and adalimumab
- total IgE (normal value: < 100 KU/l)
- serum IgE to inhalants (Phadiatop®)

Correlation between atopy and hypersensitivity reactions during therapy with three different TNFalpha blocking agents in rheumatoid arthritis.

		Adverse reactions	
		NO	YES
Total IgE (KU/l)	< 100	81.3%	18.7% §
	> 100	93.3%	6.7% §
Phadiatop	NEG	82.2%	17.8% #
	POS	88.2%	11.8% #

§ = n.s; # = n.s.

Correlation between atopy and hypersensitivity reactions during therapy with three different TNFalpha blocking agents in rheumatoid arthritis (Benucci et al).

- **Also Vultaggio et al (Int J Immunopathol Pharmacol 2008) studied 6 out of 49 pts with infusion reactions to infliximab (12%) and found no correlation with atopy, history of adverse drug reactions or urticaria.**
- **Figuereido et al (Clin Exp Rheumatol 2008;26:18) studied 35 out of 152 pts with infusion reactions to infliximab (23%), and found that the reactions "were more frequent in patients with a history of allergy ($p < 0.001$)".**

Serious skin reactions to TNF-alfa antagonists

FDA drug safety newsletter 2008;1(2):18-22

	Infliximab (Aug 1998-Aug 2006)	Etanercept (Nov 1998-Nov 2006)	Adalimumab (Dec 2002-Nov 2006)
	n = 21 reports	n = 22 reports	n = 7 reports
EM	15	13	4
SJS	5	4	2
TEN	1	4	-
SJS/TEN	-	1	-
EM/SJS	-	-	1
Patients using 1 or more concomitant medications associated with EM, SJS, and/or TEN			
	15 (71%)	15 (68%)	2 (29%)
Time to onset since first dose			
Median (days)	28	50	60
Range	4 days -18 months	5 days – 52 months	6 days – 3 years
Positive dechallenge	15	11	4
Positive rechallenge	2	3	-
Negative rechallenge	1	3	-

Hypersensitivity reactions to TNF alpha antagonists

TNF alpha antagonists are cause of hypersensitivity reactions with a fairly high frequency.

Allergological studies about infusion reactions to infliximab, in spite of their high frequency, are quite rare and gave mostly negative results.

Only a few cases of injection site reactions due to etanercept have been studied mainly with biopsies

Skin tests in cases of injection site reactions to etanercept and adalimumab are rare, in spite of their frequency

We obtained positive prick and intradermal test both at immediate and late reading with etanercept and adalimumab in patients with Injection Site Reactions and one immediate systemic reaction, but specific serum IgE was negative and also patch test.

Thanks to:

M. Severino, D. Macchia, G. Ermini, S. Testi, S. Capretti, M.L. Iorno

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...io non discuto il principio...dico solo che questo non è il momento