PRINCE OF SONGKLA UNIVERSITY

IMMUNOTHERAPY TARGETING CYTOKINES

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Cytokines & inflammation
INSTITUT PASTEUR

RHEUMATOID ARTHRITIS

The first demonstration of the efficiency of blocking a cytokine in an inflammatory disorder in humans

ANTI-TNF — chimaeric monoclonal antibody IgG1κ (cA2)
Infliximab (Remicade) - Centocor / Schering-Plough -

Elliot et al. Lancet 1994, 344, 1105

	placebo	cA2 : 2h infusion 1 mg/kg	10 mg/kg
Improvement	2 / 24	11 / 25	19 / 25

Number of swolen joints subjective scoring of pain biological parameters (CRP)

With the highest dose, clinical and biological improvements were still significant after 4 weekses

TNF R (p75) - Fcγ1 — Etanercept (Enbrel®)

Moreland et al. New Engl J Med 1997, 337, 141

After 3 months, 75% patients who got the hihest dose (16 mg/m²) had an improvement of symptoms > 20% (versus 14% in placebo group)

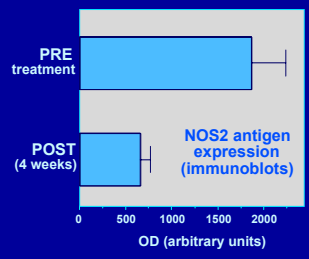
REDUCTION OF NOS2 OVEREXPRESSION IN RHEUMATOID ARTHRITIS PATIENTS TREATED WITH ANTI-TNF MAb (cA2)

Perkins et al. Arthr. Rheum 1998, 41, 2205

NOS2 EXPRESSION IN PBMC

RA Patients : 7 / 9

Control : 1 / 9



Correlation between PBMC NOS enzyme activity and the tender joint count : r = 0.93

ANTI-TNF

RHEUMATOID ARTHRITIS

Other anti-TNF antibodies

CDP571	humanized IgG4 antibody	CellTech (UK)
D2E7	human monoclonal antibody	Cambridge Antibody Technology (UK) / BASF Pharma (Germany)

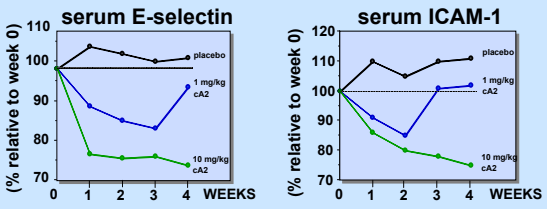
more than 470 treated patients

... Also the use of fusion proteins : TNF R - Fcγ

Etanercept (Enbrel™)	soluble p75 TNF R - Fc	Immunex (USA)
Lenercept	soluble p55 TNF R - Fc	Roche (Suisse)

DEACTIVATION OF VASCULAR ENDOTHELIUM BY ANTI-TNF THERAPY IN RHEUMATOID ARTHRITIS

Paleolog et al. Arthr. & Rheum. 1996, 39, 1082



THE EXTEND OF THE DECREASE IN SERUM E-SELECTIN AND ICAM-1 LEVELS WAS SIGNIFICANTLY HIGHER IN PATIENTS IN WHOM A CLINICAL BENEFIT OF ANTI-TNF WAS OBSERVED at WEEK +4

No effect on sVCAM-1

In parallel there was an increase in lymphocytes counts

CROHN's DISEASE

ANTI-TNF — Efficiency of the chimaeric monoclonal antibody IgG1κ (cA2) was first reported in 1995

Infliximab (Remicade™) - Centocor / Schering-Plough -

Van Dullemen et al. Gastroenterol. 1995, 109, 129

INCLUSION : 10 patients with active disease, non-responder to usual corticotherapy - infusion (2h) 10 mg/kg -

⇨ IMPROVEMENT : 8 / 10

Clinical symptoms : subjective improvement
Healing of inflammatory colon (colonoscopy)
Biological Parameters : CRP

Mean responsiveness was 4 months after one single injection

A SHORT-TERM STUDY OF CHIMERIC ANTI-TNF FOR CROHN'S DISEASE

Targan et al. N Engl J Med. 1997, 337, 1029

1 i.v. infusion cA2 over a 2h period

		Placebo n = 24	5 mg/kg n = 27	10 mg/kg n = 28	20 mg/kg n = 28
(4 weeks)	Clinical response	17 %	81 %	50 %	64 %
	remission	4 %		33 %	
	CRP (mg/L)	14.8		8.3 ±1.5	
(12 weeks)	Clinical response	12 %		41 %	

ANTI-TNF

CROHN's DISEASE

Efficiency of anti-TNF antibodies

cA2 ; Infliximab (Remicade™) - Centocor / Schering-Plough -

Present et al. N. Engl J Med 1999, 340, 1398

EFFICIENCY ON FISTULA HEALING

More than half : 62 % patients complete : 46 % patients

Rutgeerts et al. Gastroenterol 1999, 117, 761

LONG TERM EFFICIENCY

4 doses every 8 weeks : remission for half of the patients

- 13% patients made antibodies
- No serious infectious processes
- 5 patients / 771 made lymphoma

Approved FDA in 1998
One year cost : £ 12 000

CDP571, humanized (95%) anti-TNF antibody - Celltech ChiroScience, UK -

Stack et al. Lancet 1997, 349, 521

Inclusion : 31 patients

1 x 5 mg/kg

6 remissions / 21 (29%)

Sandborn et al Gut 1999, 45, abstract 133

Inclusion : 169 patients

1 x 10 or 20 mg/kg every 8 -12 weeks during 6 months

64% positive response with the lower dose

ALLERGY & ASTHMA

MAb Humanized IgG1 ANTI-IL-5 SB-240563

Clinical Study in allergic and asthmatic patients (phase II)

1 x en i.v.

Long term inhibition of circulating eosinophils

BUT No effect on :

early and late response to allergen challenge (bronchoconstriction)

ANTI-IL-9 (Magainin Pharm.)

ANTI-IL-4 (SB-240683) / Soluble IL-4 receptor (Immunex)
IL-4 receptor antagonist (BAY 16-996)

PSORIASIS

PHASE I / II STUDIES - Abgenix, Inc.

MAb HUMAIN ANTI-IL-8

45 patients

ABX-IL8
4 x every 3 weeks

	Psoriasis area severity index ▯ 25% improvement	▯ 50% improvement
1 ou 3 mg/kg	58 %	21 %
0.3 mg/kg	20 %	0 %
placebo	0 %	0 %

SYSTEMIC LUPUS

Llorente L, ... , P. Galanaud & D. Emilie Arthr. Rheum. 2000, 43, 1790

MURINE MAb ANTI-IL-10 ⇨ Cutaneous lesions and joints symptoms improved in all patients

20 mg/day i.v.
during 3 weeks

6 patients	SLE Index	Prise de prednisone
day 1	8.8 ± 0.9	27.9 ± 5.7 mg/day
day 21	3.7 ± 0.7	
2 months	1.5 ± 0.8	
6 months	1.3 ± 0.8 (inactive disease for 5/6 patients)	9.6 ± 2.0 mg/day

At D+10 :

significant reduction of plamsa levels of sIL-2R et sVCAM1
+
Increased levels of IL-1ra
+
Reduction of spontaneous *in vitro* production ofIL-10

KIDNEY TRANSPLANTATION

ANTI-IL-2Rα (CD25)

Results of 2 phase III studies (535 patients)
(+ cyclosporine + prednisone +/- azathioprine)

ZENAPAX
(humanized IgG1 Antibody)
Lab. Roche
FDA 1997

1 mg/kg :
1 x T-24 h
5 x every 14 days

	TREATED	PLACEBO
Graft rejection (6 months)	6.0 %	11.6 %
mortality - 6 months	0.4 %	3.7 %
mortality - 1 year	1.5 %	4.4 %
side effects	39.9 %	44.4 %
infectious events	68 %	72 %

SIMULECT
(Chimearic antibody IgG1κ)
Novartis
FDA 1998

Rejection (12 months) 31 % 45 %

Anti-murine antibodies : frequency = 3,5 %

GLAUCOMA SURGERY

PHASE I / II ASSAYS - Cambridge Antibody Technology

MAb HUMAIN ANTI-TGFβ2

- Healing process ?

No adverse effect

REDUCTION OF NEW SURGERY REQUIREMENT