

ANTI-CYTOKINE THERAPY

TNF IN RA

- INCREASED IN SYNOVIAL FLUID
- PRODUCED BY
SYNOVIOCYTES/MACROPHAGE
- STIMULATES IL-1, IL-6 PRODUCTION
- STIMULATES MMP PRODUCTION
- INFLAMMATORY MEDIATOR AND
FATIGUE

TNF INHIBITORS IN RA

- PRECLINICAL DATA
- TRANSGENIC MODELS
- ANIMAL MODELS
- CLINICAL EXPERIENCE

ANTI-TNF RX

- Monoclonal antibodies
 - infliximab (chimeric)
 - D2E7 (human)
- Soluble receptors
 - etanercept (p75)
 - lenercept (p55)
 - pegylated receptors

INFLIXIMAB

- CHIMERIC MAB
- IV INFUSION
- RAPID RESPONSE

INFLIXIMAB IN RA

LANCET 344:1105-1110, 1994

- DESIGN: RCT, PLACEBO CONTROLLED
- 1 INFUSION, 4 WEEK FOLLOWUP
- DRUG: cA2 - CHIMERIC IgG1 MAB
- DOSES: 1.0 MG/KG; 10.0 MG/KG
- POPULATION: 73 RA, DMARD FAILURES
- RESULTS: PAULUS RESPONSE

PLACEBO	8%
1.0 MG/KG	44%
10.0 MG/KG	79%

DECREASE IN CRP

INFLIXIMAB IN RA

NEJM 343:1594,2000

- Study design: 54 wk RCT, Dosing 0,2,6 and then 4 or 8 wks
- Population: 428 pts with active RA, mean disease 10.4 yrs
- MTX dose (median) 16 mg/wk
- Drug: infliximab 3 mg/kg q 4,8 wk
- 10 mg/kg q 4,8 wk
- Response

	ACR 20	ACR 50	ACR 70
• Placebo	17%	8%	2%
• 3 mg/kg q 8 w	42	21	10
• 3 mg/kg q 4 w	48	34	17
• 10 mg/kg q 4w	59	38	19
• 10 mg/kg q 8 w	59	39	25

- Withdrawals infliximab 21%, placebo 50%
- Positive effects on radiographs in erosions and narrowing with all doses of infliximab as compared to mtX alone

ETANERCEPT

- P75 SOLUBLE RECEPTOR
- SQ ADMINISTRATION
- 25 MG.> 10 MG DOSE
- 3 PLACEBO CONTROLLED STUDIES
- ONSET OF ACTION- 2-4 WEEK

sTNFr IN RHEUMATOID ARTHRITIS

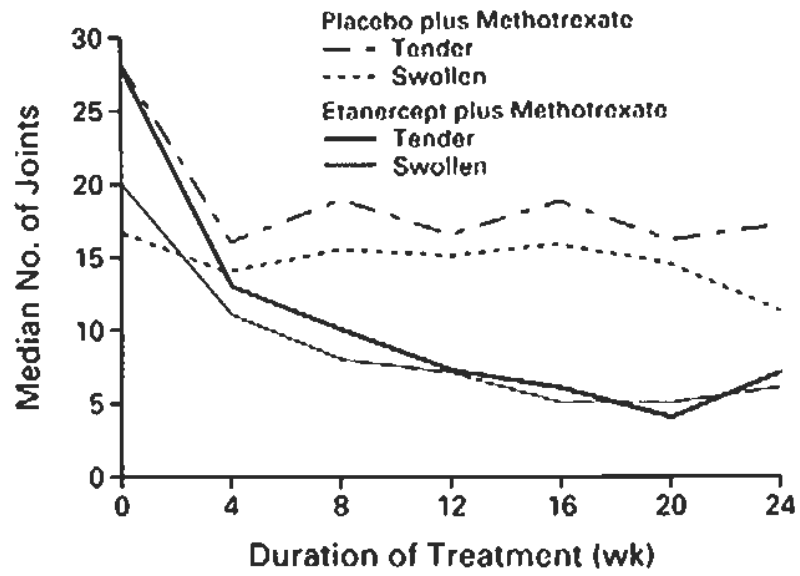
NEJM 337:141-147,1997

- No. patients: 180, with active RA
- Design: 12 wk, placebo controlled RCT
- Drug: p75 sTNFr (0.25, 2.0, 16.0 mg/m²) sq 2/wk
- Demographics: Disease duration: 77% > 5 years
Swollen joints, 26; tender joints, 30
- Response: ACR Criteria
sTNFr, 16.0 mg/m² (75%); placebo (14%)
- AE: injection site reactions, no antibodies to sTNFr detected

Etanercept+MTX

NEJM 340:253-259,1999

- Study design: 24 wk RCT
- Population: 89 pts with active RA (13 yr)
- chronic MTX Rx > 3 yrs MTX dose 18 mg (12.5-25 mg)
- Drug: etanercept 25 mg sq 2/wk vs placebo
- Response etanercept+mtx pla+mtx
- ACR 20 71 27%
- ACR 50 39 3
- ACR 70 15 0
- Withdrawals 3% 20%
- AE's injection site reactions



ANTI- TNF:ADVERSE EVENTS

- INFECTIONS
 - BACTERIAL SEPSIS
 - OPPORTUNISTIC INFECTIONS
 - MTB
 - ATYPICAL MYCOBACTERIUM
 - FUNGAL
 - PCP
 - LISTERIA
- CUTANEOUS VASCULITIS
- DEMYELINATING SYNDROMES
- APLASTIC ANEMIA
- LUPUS LIKE SYNDROMES

ANTI-TNF THERAPY: QUESTIONS

- LONG TERM EXPERIENCE
 - SAFETY, EFFICACY
 - DOSING REGIMENS
- INFECTION RISK
- RISK OF LYMPHOPROLIFERATIVE DISEASE
- AUTOANTIBODIES
 - SLE, ANTI-PHOSPHOLIPID SYNDROME
- DRUG ANTIBODIES-ALLERGIC RXTS, TOLERANCE
- COST

Anti-TNF Rx in Rheumatology

- RANDOMIZED TRIAL
 - JRA
 - Psoriatic Arthritis
- OPEN EXPERIENCE
 - Ankylosing Spondylitis
 - Wegener's
 - Vasculitis
 - Adult Still's Disease
 - Scleroderma
 - Myositis
 - Periodic fever
 - Behcet's

ANTI-TNF α Rx: Other Diseases

- Myelodysplastic Syndromes
- Uveitis
- Graft vs. Host
- Pulmonary Fibrosis/Sarcoidosis
- Diabetes
- Endometriosis, Prostatitis
- Hepatitis C
- CHF