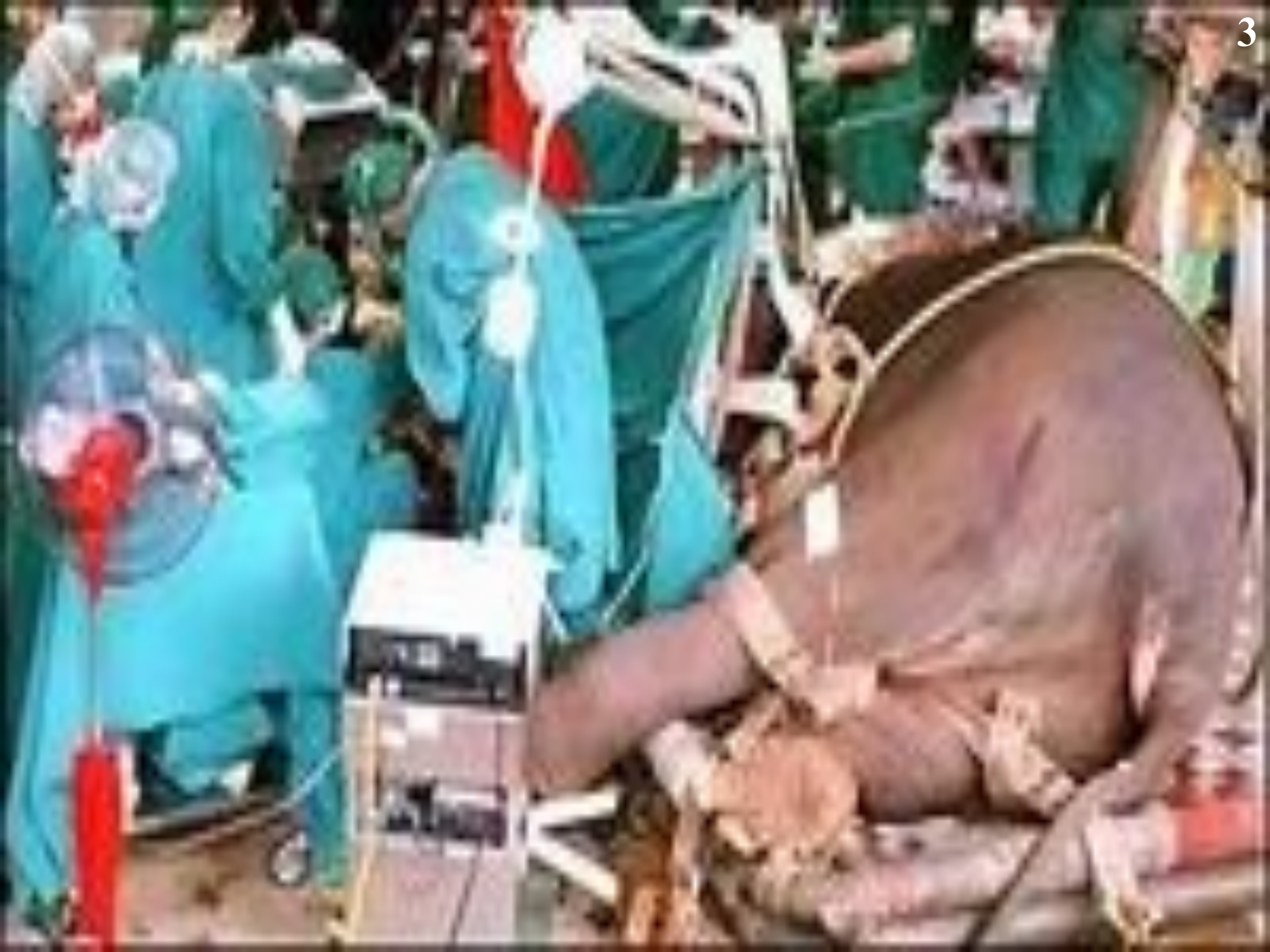
- בן 45 עם כאבי פרקים סימטרים עם נפיחויות, קשיון בוקר מעל שעה חודשיים
- RF חיובי, ESR 70, CRP 10 עם נורמה פחות מ 0.5 מג'\דל'
- וולטרן לא עזר
- באישפוז קיבל זריקת סינקטן (ACTH) וחל שיפור ניכר בכאבי פרקים
- קיבל עירוי סטרואידים במינון של סולומדרול 50 מג' לעירוי ליום
- הוחל טיפול משולב ע"י זריקות מטוטרקסט 15 מג' לשבוע, פלקוניל 400 מג' ליום, סלזופירין 2 ג' ליום מלווה כדורי פרדניזון במינון 10 מג' ליום
- כעבור שנה התלקחות דלקת פרקים, הופסק פלקוניל וסלזופירין והוחל טיפול ב Remicade נוגדנים לTNF אלפא
- לאחר תקופת הפוגה של שנה התלקחות חדשה, הופסק רמיקאיד
- הוחל טיפול ב Enbrel זריקות תת עוריות פעמיים בשבוע (קולטן נמס של TNF אלפא)
- כעבור שנתיים התלקחות חדשה, קיבלה טיפול ב נוגדנים ל CD 20 של B-cells

Antirheumatic therapy

Risk

Benefit

Empathy



Nonpharmacologic therapy

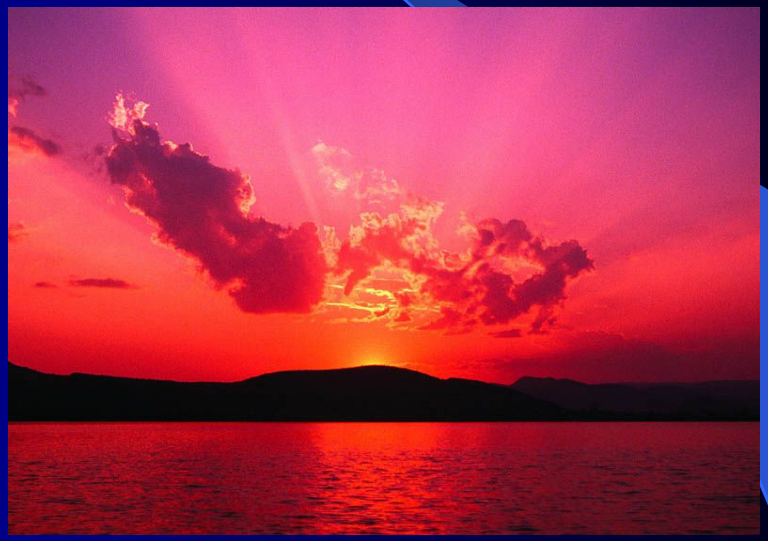
Education

Cognitive behavior therapy

- Relaxation
- Stress management

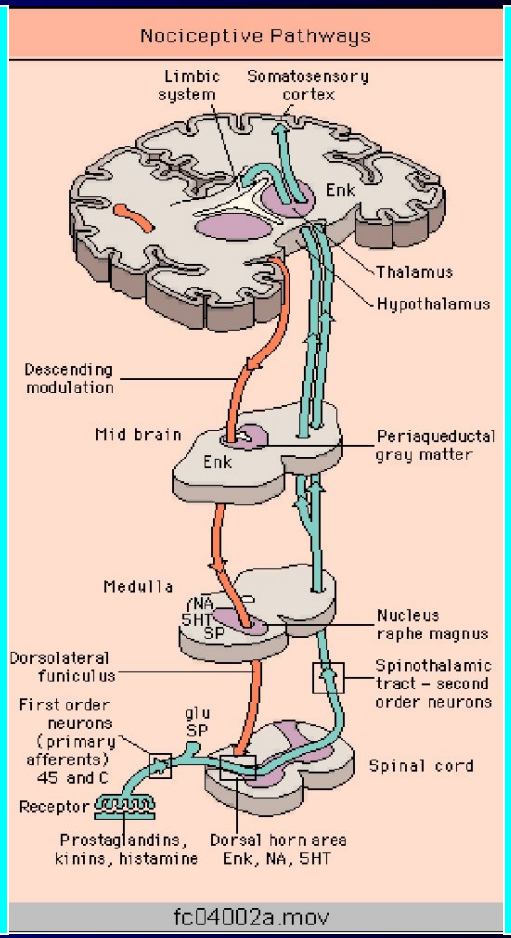
Nonpharmacologic therapy

- Rest
- Exercise
- Light
- Heat
- Cold
- Hydrotherapy
- Manipulation
- Electricity
- US



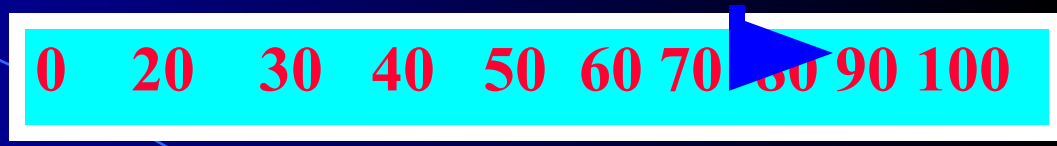
Pharmacotherapy: Analgesics

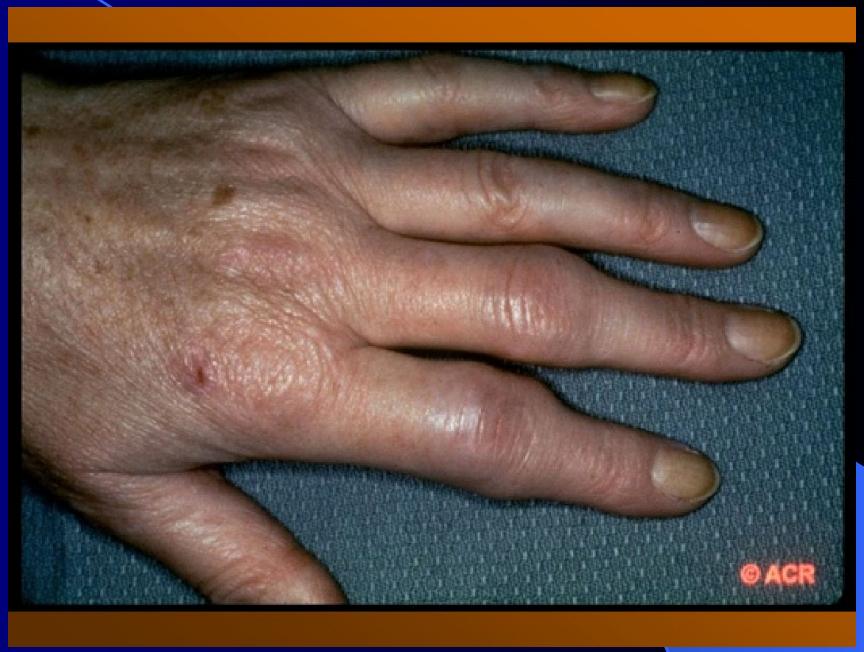
- Paracetamol
- Dipyrone (Optalgin)
- Oint Zostrix (Capsaicin)
- Amitriptillin, Carbamazepine
- Codein
- Tramadol
- Oxycodone
- Durogesic (Phentanyl) transdermal patches

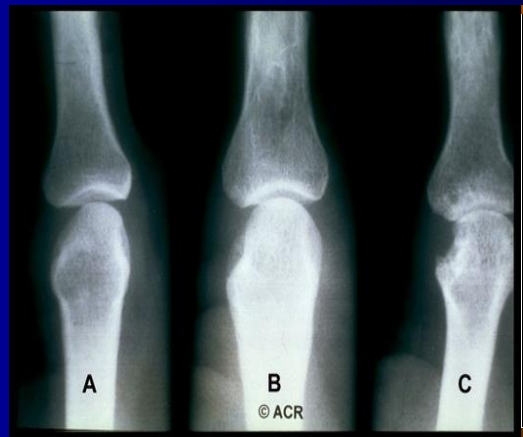


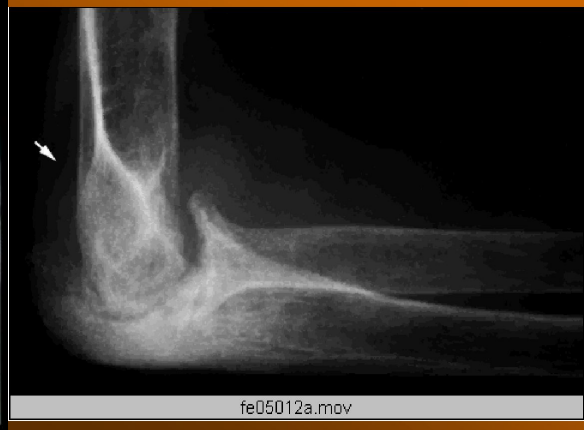
Outcome Measures in Rheumatic Diseases

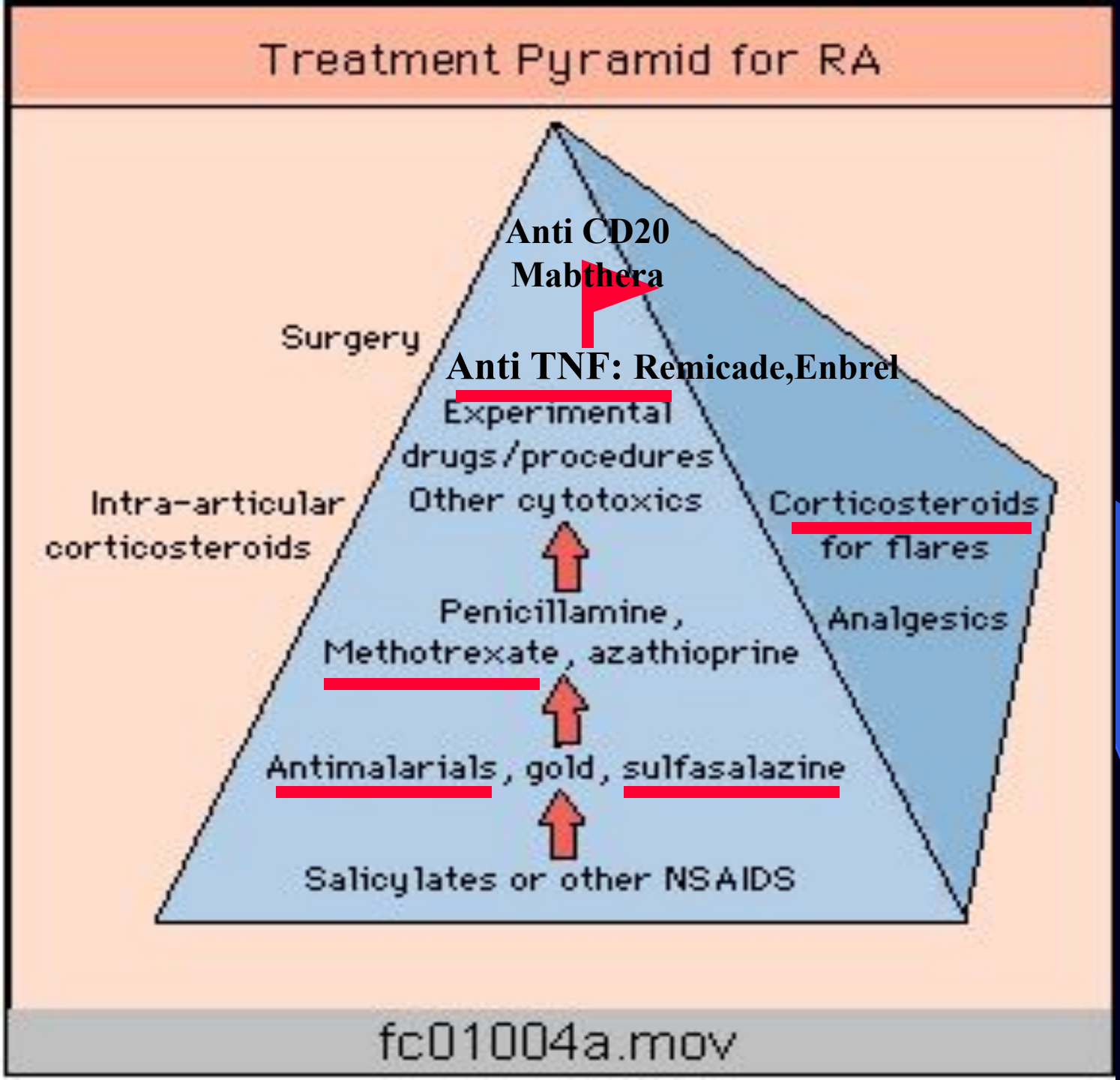
- Pain assessment VAS
- Tender joint count
- Swollen joint count
- Disability HAQ, WOMAC
- C-reactive protein
- ESR
- Imaging: X-Ray, CT
  - Erosion score
  - Joint narrowing










Treatment Pyramid for RA
Anti CD20
Mabthera
Surgery
Anti TNF: Remicade,Enbrel
Experimental
drugs/procedures
Other cytotoxics
Intra-articular
corticosteroids
Corticosteroids
for flares
Analgesics
Penicillamine,
Methotrexate, azathioprine
Antimalarials, gold, sulfasalazine
Salicylates or other NSAIDS
fc01004a.mov

NSAID's: Processes influenced by NSAID's

- **Inflammatory mediators:**
  - **Prostaglandin synthesis**
  - **Leukotriene synthesis**

→ **Pain reduction**

- **Neutrophil function:**
  - **Superoxyde production**
  - **Lysosomal enzyme release**

→ **Inflammation reduction**

- **Immunocompetent cell function:**
  - **Lymphocyte activity**
  - **RF and NO production**
  - **Cytokine production**

→ **Disease modifying effect: preventing joint damage**

NSAID's inhibition of COX1 and COX2

- Cyclooxygenase 1 (COX1) provides constant
  - gastric mucose production
  - gastro-duodenal bicarbonate
  - gastric blood flow and tissue repair
  - renal blood flow
  - platelet aggregation
- Cyclooxygenase 2 (COX2) is induced only by
  - IL-1, TNF-alpha, LPS
  - promotes synthesis of proinflammatory PG

NSAID's inhibition of COX1 and COX2

NONSELECTIVE INHIBITORS of COX

- Indomethacin, Aspirin, Piroxicam, Ibuprophen, Diclofenac, Piroxicam, Naproxen

PREDOMINANT COX2 INHIBITORS

- Nabumetone, Etodolac, Nimesulide

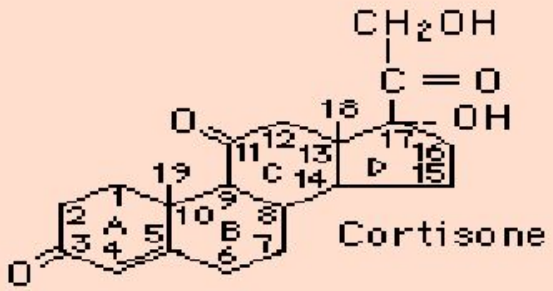
SELECTIVE COX2 INHIBITORS

- Celecoxib (Celcox), Rofecoxib (Vioxx), Etoricoxib (Arcoxia)

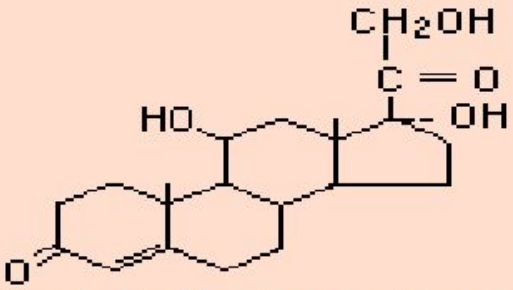
Adverse reactions to NSAID

- **Gastrointestinal:** GER, peptic ulcer, perforation (nonselective)
- **Hepatic:** transaminasemia, cholestasis
- **Renal:** acute renal failure, interstitial nephritis, hypeK
- **Hematologic:** cytopenia, red cell aplasia, hemolysis (nonselective)
- **Cutaneous:** urticaria, photosensitivity, erythema multiforme, TEN
- **Respiratory:** bronchospam, pneumonitis
- **CNS:** headache, dizziness, aseptic meningitis (ibufen, sulindac)
- **Exacerbation of hypertension** (common)
- **Increased rate of vascular events**

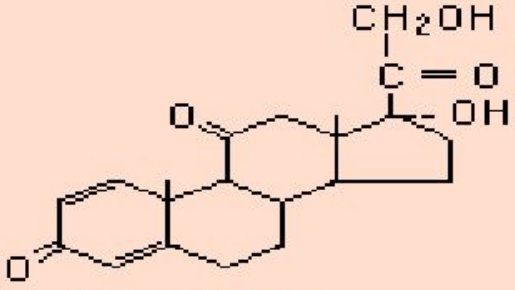
Structure of Some Natural and Synthetic Corticosteroids



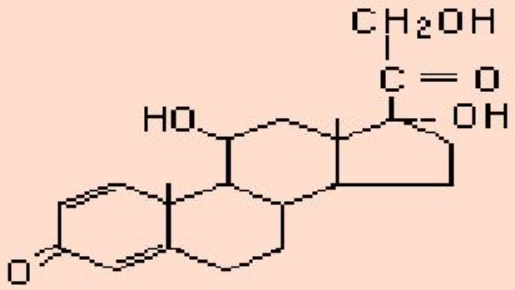
Cortisone



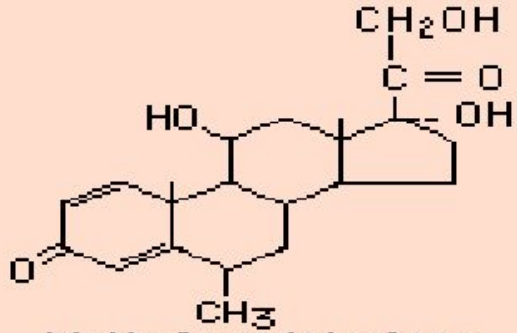
Cortisol (hydrocortisone)



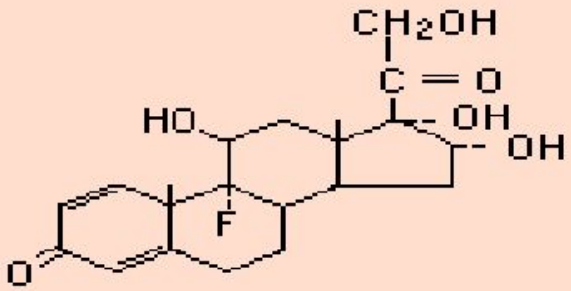
Prednisone



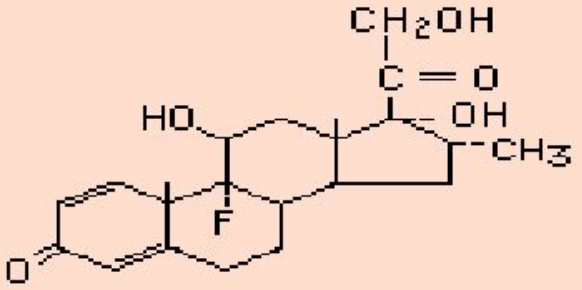
Prednisolone



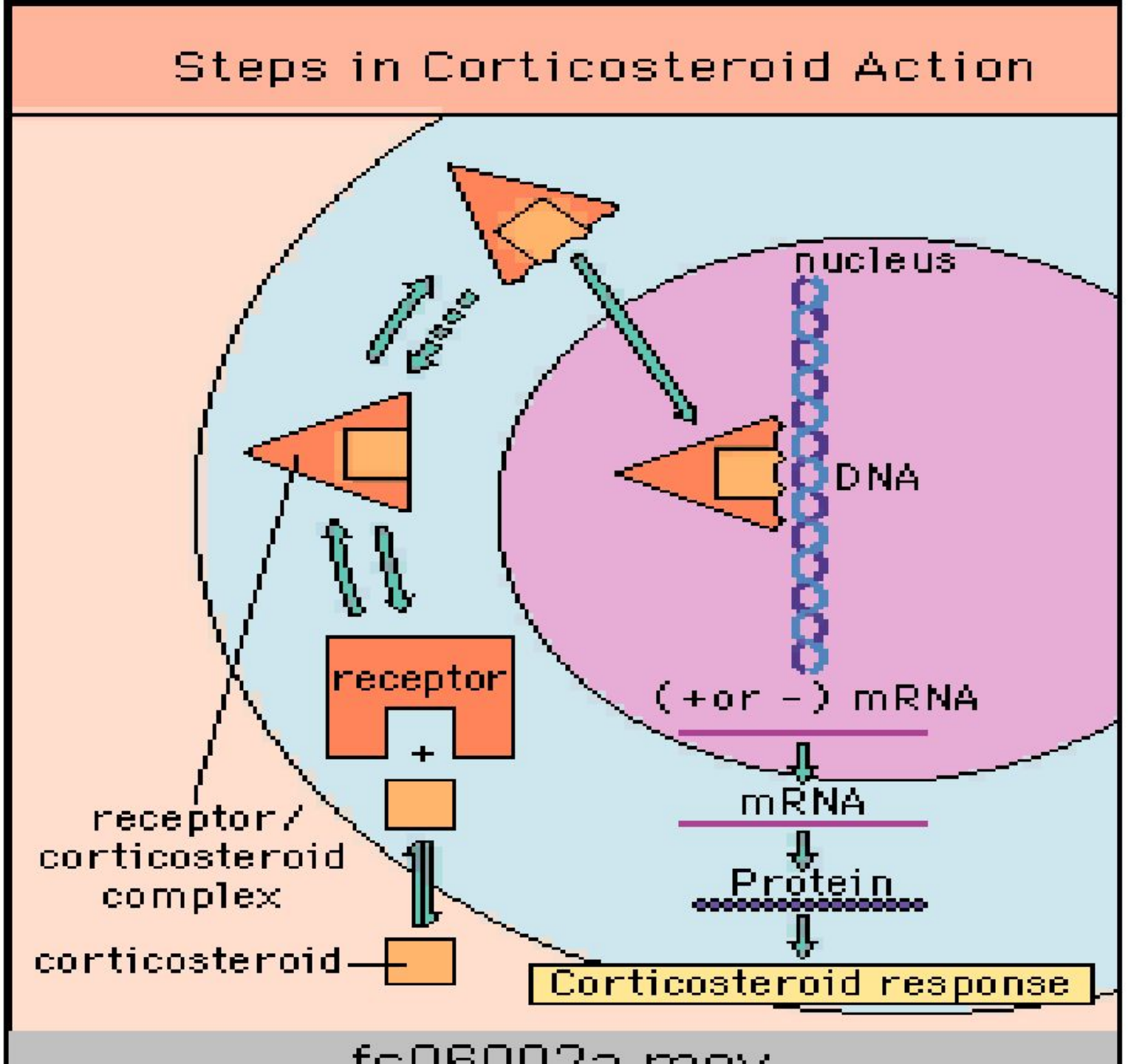
Methylprednisolone



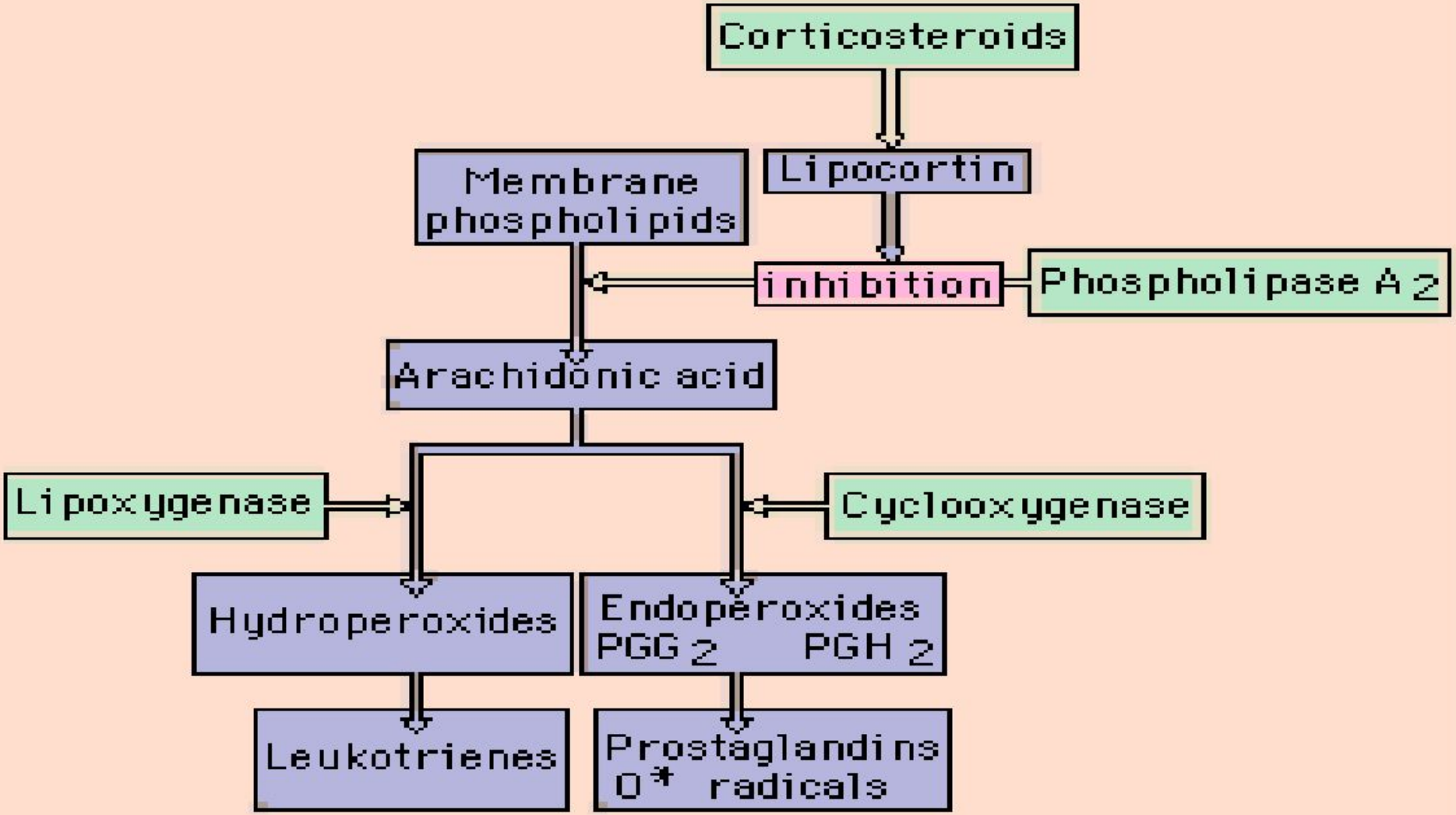
Triamcinolone



Dexamethasone


Steps in Corticosteroid Action
nucleus
DNA
(+or -) mRNA
receptor
+
receptor/
corticosteroid
complex
corticosteroid
mRNA
Protein
Corticosteroid response

Action of Corticosteroids



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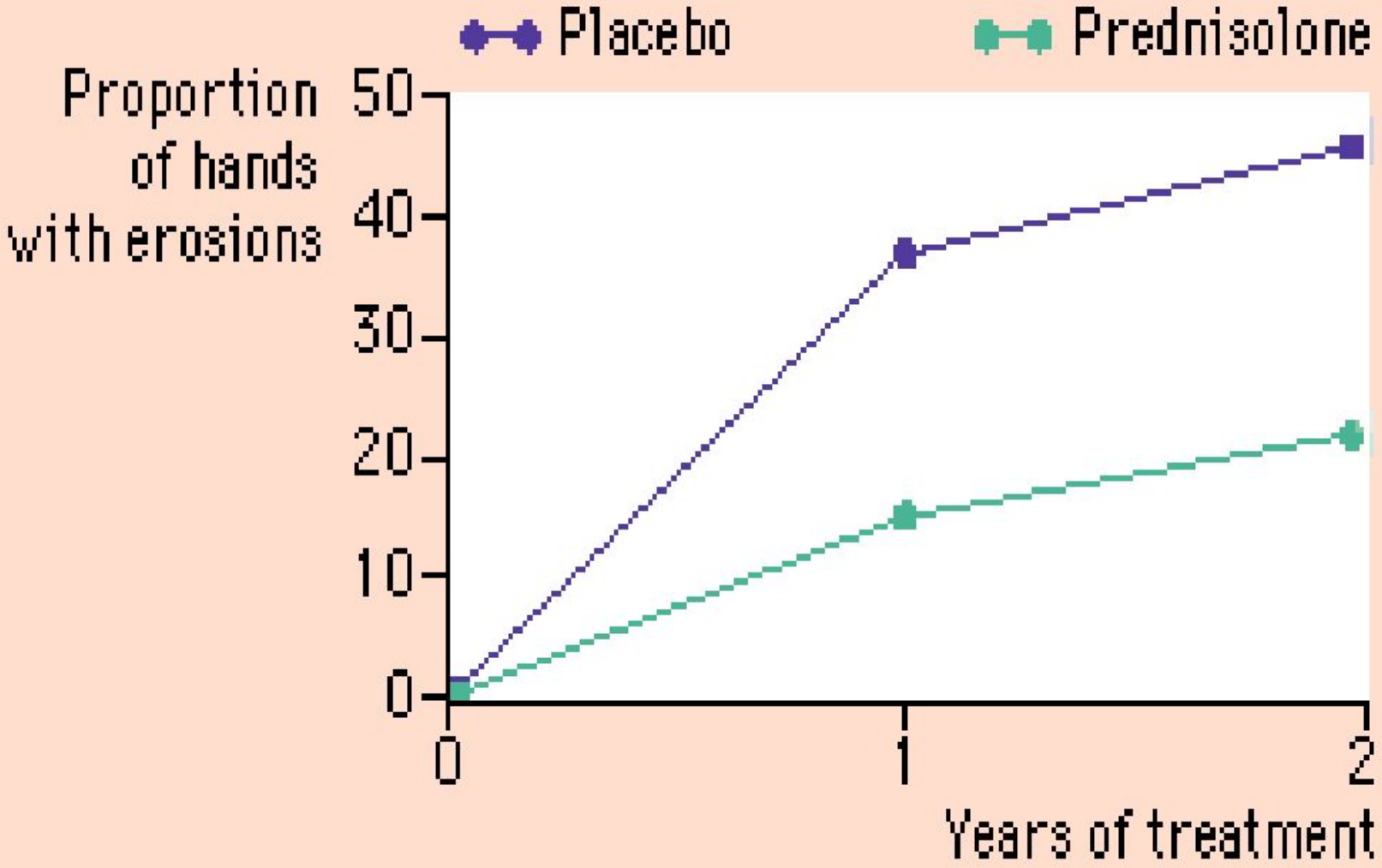
Some Commonly used Corticosteroids

Duration of action	Corticosteroid	Equivalent oral or intravenous doses (mg)	Relative sodium-retaining action
Short ($t_{1/2}$ 8–12 hours)	Cortisone	25	0.8
	Cortisol	20	1
Intermediate ($t_{1/2}$ 12–36 hours)	Prednisone	5	0.8
	Prednisolone	5	0.8
	Methylprednisolone	4	0.5
	Triamcinolone	4	0
Long ($t_{1/2}$ 36–72 hours)	Paramethasone	2	0
	Dexamethasone	0.75	0
	Betamethasone	0.60	0

fc06004a.mov

Erosive Progression with Prednisolone



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Adverse Effects of Systemic Corticosteroid Therapy	
Metabolic	obesity glucose/protein metabolism electrolyte imbalance enzyme induction
Predisposition to infection	
Musculoskeletal	myopathy osteoporosis osteonecrosis tendon rupture corticosteroid withdrawal syndrome
Gastrointestinal	peptic ulcer disease pancreatitis
Ophthalmic	cataract glaucoma
Central nervous system	psychosis depression benign intracranial hypertension
Dermatologic	acne striae alopecia bruising skin atrophy
Growth retardation	
Hypothalamic–pituitary–adrenal axis suppression	

fc06007a.mov

Adverse Effects of Pulse Methylprednisolone Therapy

Sudden death/ventricular dysrhythmia
Severe infection
Transient arthralgia/synovitis
Hyperglycemia
Pancreatitis
Gastrointestinal bleeding
Acute psychosis

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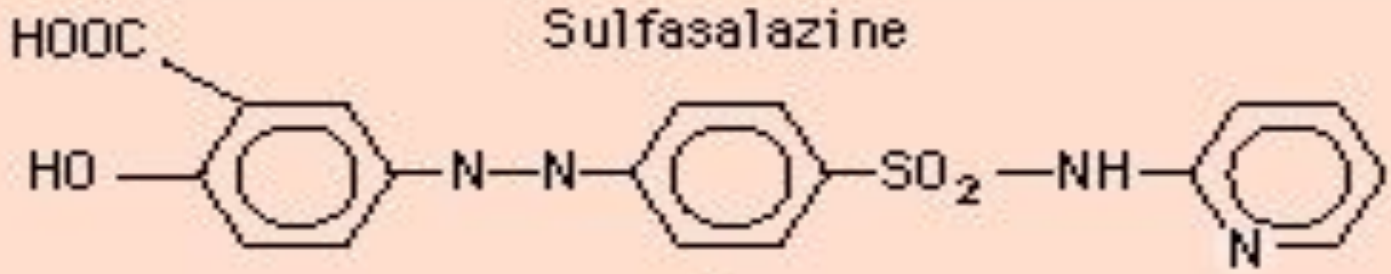
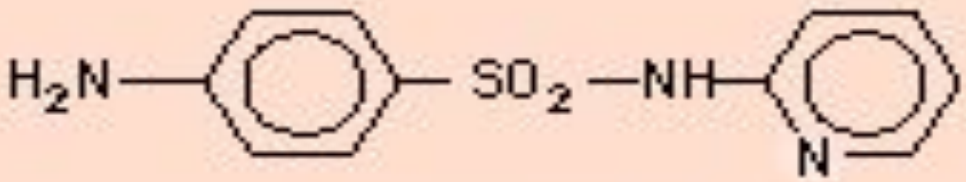
Sulfasalazine and its Metabolites

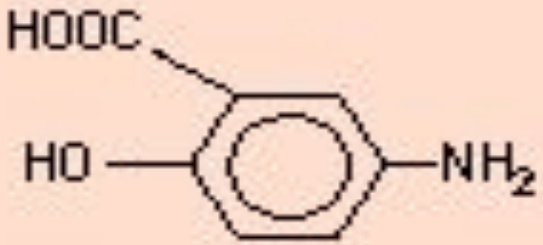


Sulfasalazine

Cleavage by colonic bacteria



Sulfapyridine



5-Aminosalicylic acid

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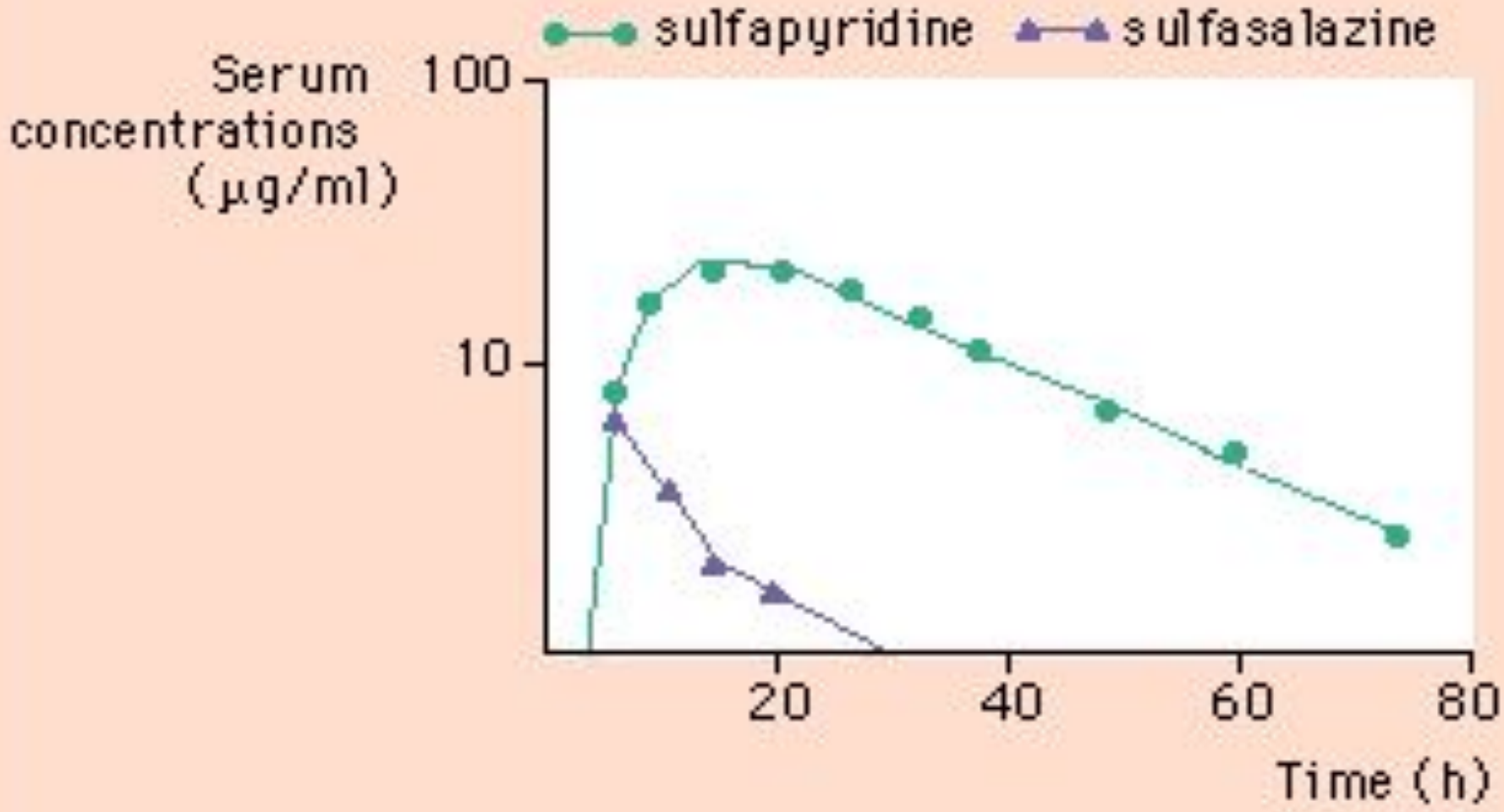
Pharmacokinetics of Sulfasalazine and Sulfapyridine



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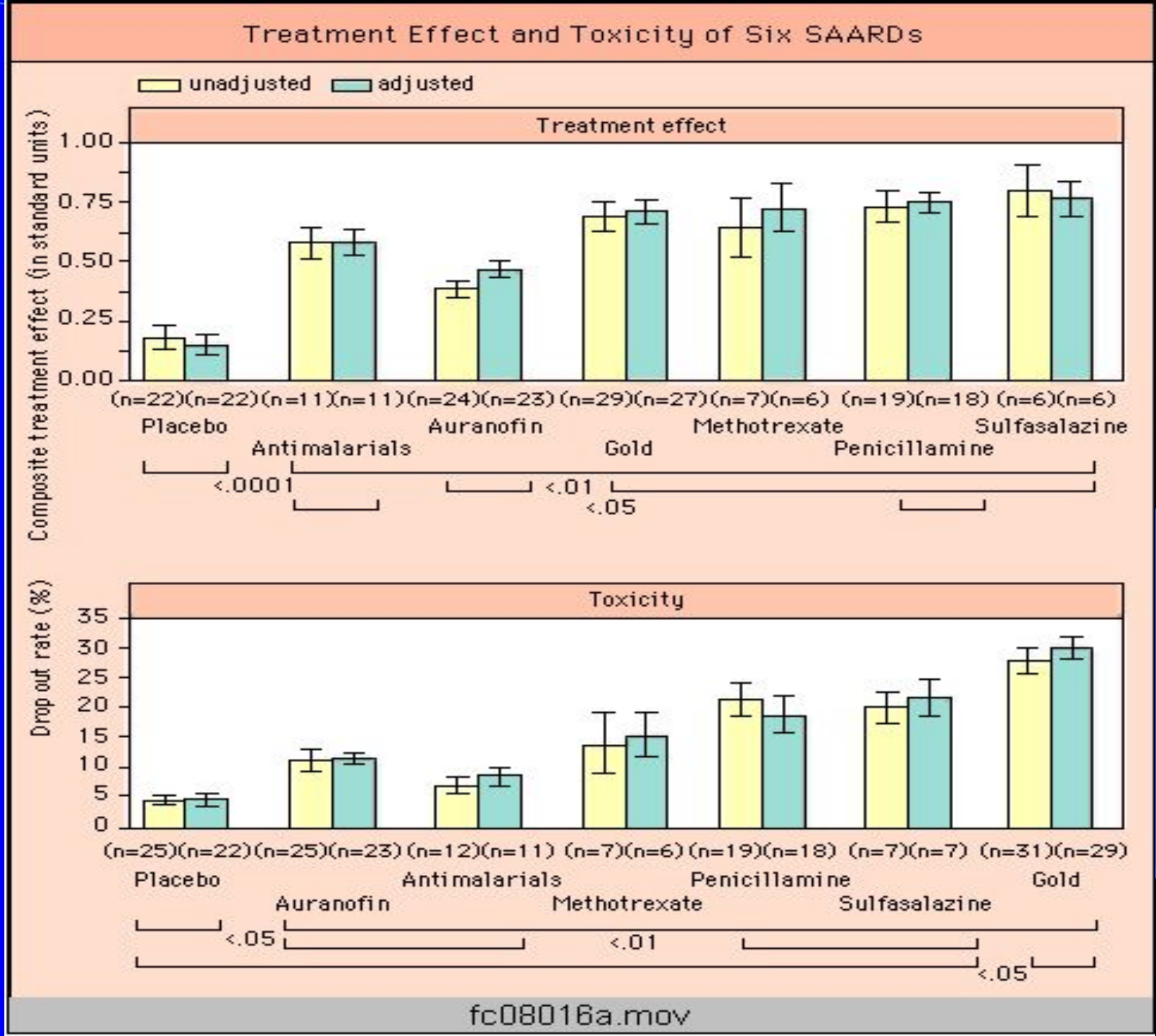
Treatment Effect and Toxicity of Six SAARDs
unadjusted
adjusted
Treatment effect
Composite treatment effect (in standard units)
1.00
0.75
0.50
0.25
0.00
(n=22)(n=22)(n=11)(n=11)(n=24)(n=23)(n=29)(n=27)(n=7)(n=6)(n=19)(n=18)(n=6)(n=6)
Placebo
Antimalarials
Auranofin
Gold
Methotrexate
Penicillamine
Sulfasalazine
<.0001
<.01
<.05
Toxicity
Drop out rate (%)
35
30
25
20
15
10
5
0
(n=25)(n=22)(n=25)(n=23)(n=12)(n=11)(n=7)(n=6)(n=19)(n=18)(n=7)(n=7)(n=31)(n=29)
Placebo
Auranofin
Antimalarials
Methotrexate
Penicillamine
Sulfasalazine
Gold
<.05
<.01
<.05
fc08016a.mov

Toxicity of Sulfasalazine	
Common adverse effects	
Gastrointestinal	Nausea, vomiting, malaise, anorexia, abdominal pain, dyspepsia, indigestio
CNS	Headache, pyrexia, light headedness, dizziness.
Less common and some serious adverse effects	
General	Hypersensitivity reactions.
Skin	Rash (pruritic, macular papular) 1–5%, alopecia, Stevens–Johnson syndrome and related serious skin disorders. Rarely serum sickness.
Hepatic	Hepatic enzyme elevations; acute hepatic reactions; more serious damage has been described.
Lung	Fibrosing alveolitis; rarely reversible pulmonary infiltrates accompanied by eosinophilia, fever and weight loss have been described.
Hematologic	Leukopenia (1–3%); thrombocytopenia (less frequent than leukopenia); hemolysis, MCV increased; methemoglobinemia; aplastic anemia; agranulocytosis.
Nervous system	Irreversible neuromuscular and CNS effects rarely reported.
Kidney	Serious kidney damage has occurred rarely.

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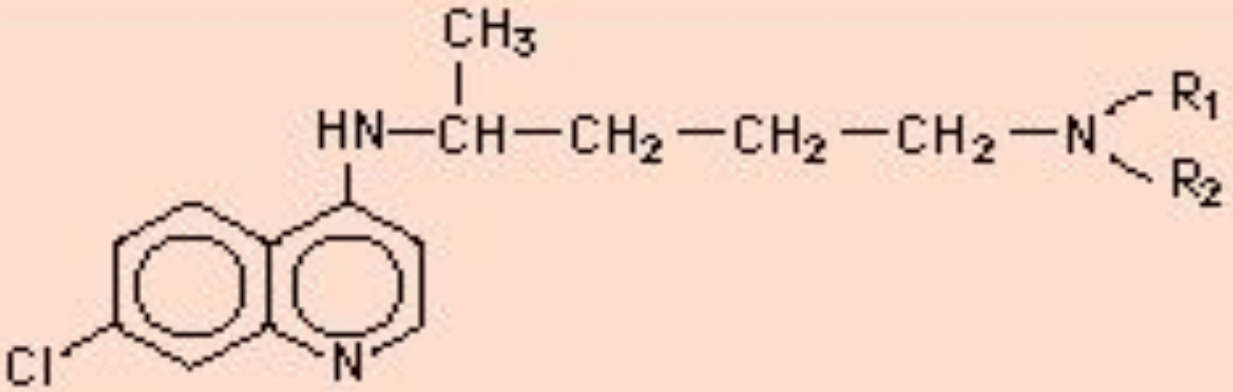
Antimalarials Used in Rheumatic Diseases



	R_1	R_2
Chloroquine	CH_2CH_3	CH_2CH_3
Hydroxychloroquine	CH_2CH_3	CH_2CH_2OH
Desethylchloroquine	CH_2CH_3	H
Desethylhydroxychloroquine	H	CH_2CH_2OH
Bisdesethylchloroquine	H	H

fc08011a.mov

Toxicity of Antimalarials in RA and SLE

Organ	Notes
Mucocutaneous	Pruritic and urticarial rash; stomatitis.
Gastrointestinal	Anorexia; nausea; vomiting; abdominal pain, diarrhea.
CNS	Dizziness; tinnitus; headache.
Eyes	Blurred vision and accommodation difficulty, especially early in therapy which resolves with continued therapy. Photophobia. Retinal damage (bull's eye retinopathy).
Pregnancy	Crosses placenta; theoretically hazardous therefore avoid if possible; some cases of fetal abnormalities reported but little data.
Overdose	Chloroquine more dangerous; cardiorespiratory failure occurs rapidly; emphasize importance of keeping medication away from children.

fc08012a.mov

Mechanisms of Action

SAARD	Active agent(s)	Mechanism	Reference
Azathioprine	6-Thioinosinic acid 6-Thioguanylic acid	Interferes with adenine and guanine ribonucleosides	5-10
Chlorambucil	Phenylacetic acid mustard (metabolite)	Cross-links DNA	7-10
Cyclophosphamide	Phosphoramide mustard (metabolite)	Cross-links DNA	5-12
Cyclosporin	Parent compound and up to 15 metabolites	Suppresses IL-2 synthesis and release Suppresses T-cell response and interaction	10-13
Methotrexate	Parent compound and metabolites, including 7-OH-methotrexate and methotrexate polyglutamates	Inhibition of dihydrofolate reductase, thymidylate synthetase and phosphoribosyl-aminoimidazole-carboxamide-transformylase activity IL-1 and IL-2 suppression	14-16
Tetracyclines	Parent compound	Metalloproteinase inhibition: possible effects on PMN and lymphocyte function	2-4

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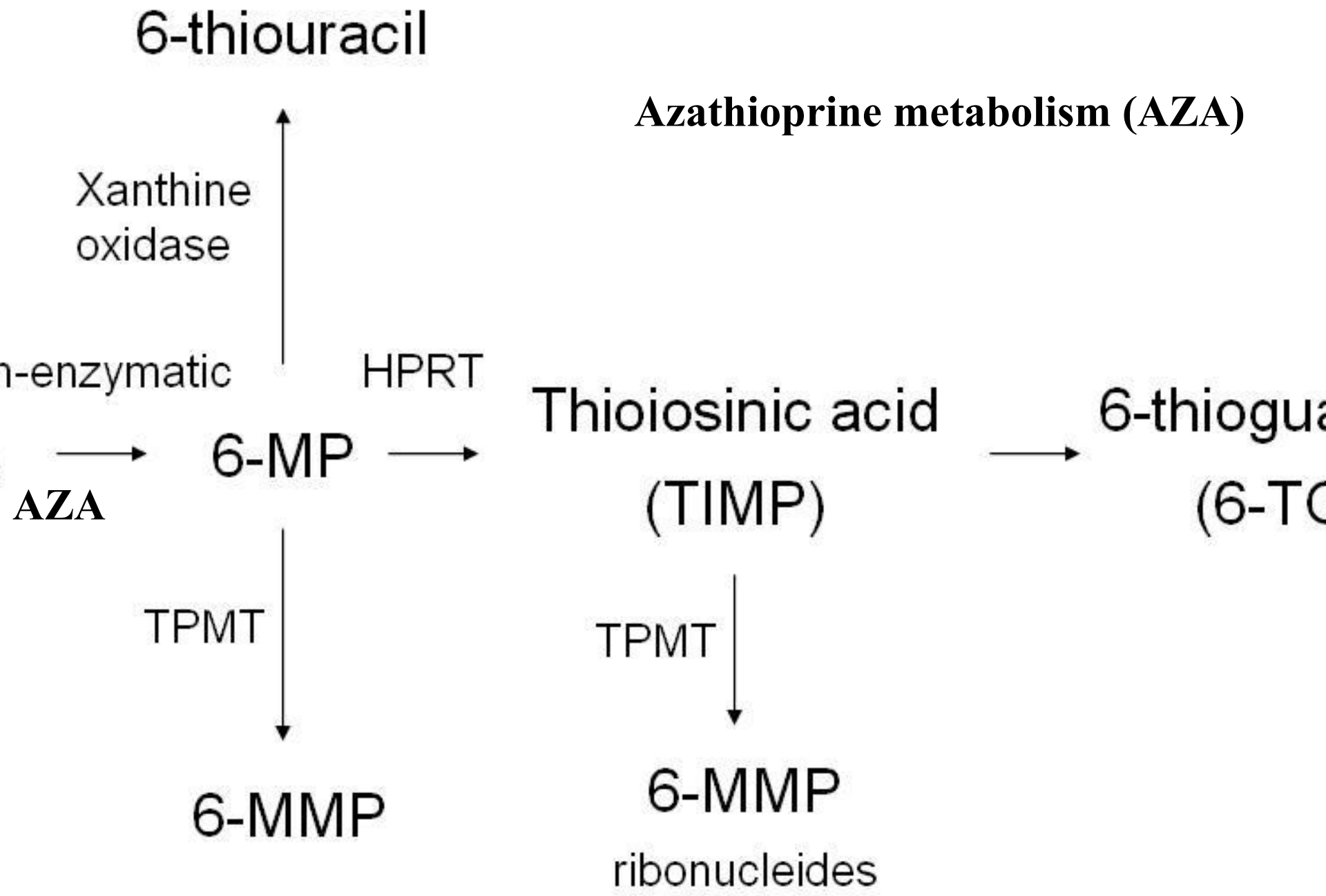
Azathioprine metabolism (AZA)



Summary of Performance of Gold Compounds in RA

Injectable gold compounds

1. Intramuscular gold 10-50mg/week for 1-2 years is effective but no dose-response relationship is evident.
2. Response cannot be predicted.
3. Excellent responses occur in 20-35% of patients after 6-12 months treatment.
4. Excellent responses are sustained beyond 1 year in only 50%.
5. Sustained remission occurs in very few patients.
6. Gold slightly retards radiologic progression of RA.
7. Only about 20% of patients are still taking gold after 4 years therapy.
8. Gold has similar efficacy to D-penicillamine, sulfasalazine, azathioprine and methotrexate and may be slightly more efficacious than antimalarials.

Auranofin

1. Auranofin 6mg/day is superior to placebo and improves RA over 6-9 months, is slightly less effective than aurothiomalate and D-penicillamine (750mg/day) but causes fewer serious adverse effects than these SAARDs.
2. Remissions are less common than with aurothiomalate and improvements are usually not sustained.
3. Diarrhea is dose-limiting.

fc08005a.mov

Toxic Effects of Gold Compounds

Organ	Notes
Mucocutaneous (60–80% of toxicity)	Dermatitis and mouth ulcers; pruritus commonest; rashes usually erythematous and macular but rarely can exfoliate.
Vasomotor	Within minutes usually of aurothiomalate injection and include sweating, flushing, nausea, faintness, hypotension and weakness; malaise, fatigue and myalgia can follow injections.
Kidney	Transient and minor proteinuria commonly; occasional membranous glomerulonephropathy; rarely nephrotic syndrome which usually recovers in months to years; weak association with HLA-DR3/HLA-B8.
Blood	Eosinophilia occurs often prior to a toxic reaction. Neutropenia due to gold, as opposed to RA itself, is suggested by rapid or progressive fall in neutrophils. Thrombocytopenia (occurs in 1–3%); usually minor but can be precipitate and serious. Aplastic anemia rare but has a high fatality rate. Recombinant DNA-derived human hemopoietic growth factors have improved outcome somewhat.
Lung	Hypersensitivity pneumonitis reversible on cessation of gold. Case reports of bronchiolitis obliterans.
Liver	Case reports of cholestasis, fatty and inflammatory cell infiltrates.
Bowel	Case reports of enterocolitis with some deaths.
Nervous system	Case reports of peripheral and cranial neuropathies, Guillain–Barré syndrome, encephalopathy, myokymia

fc08007a.mov

Leflunomide (Arava)

- Isoxazole derivate
- Active metabolite A77 1726

Immunological efects of leflunomide

- inhibits dihydro-orotate-dehydrogenase(pyrimidine syn)
- T-cell arrest by activation p53
- inhibits B-cell proliferation and AB-production
- RF reduction
- rapidly inhibits NF-kB and acute phase response
- Inhibits chemotaxis of neutrophils

Double-Blind Trials of SAARD Combinations

Combination	Outcome	Comparator	N
HCQ + SSZ	=	HCQ or SSZ	91
HCQ + SSZ	<	Dpen	56
MTX + AF	=	MTX or AF	335
MTX + AZA	=	MTX	209
HCQ + Dapsone	=	HCQ or Dapsone	80
HCQ + MTX	=	MTX	141
HCQ + Gold	±>	Gold or placebo	101
MTX + CSA	≥	MTX	148
CQ + MTX	≥	MTX	82
HCQ + SSZ + MTX	>	MTX or HCQ + SSZ	100

fc09005a.mov

Different Types of Biological Treatments

Treatment type	Examples
Monoclonal antibodies	
Murine antibodies	Anti-ICAM-1 monoclonal antibody, BIRR
Chimeric antibodies	Anti-TNF-α monoclonal antibody, cA2
Humanized antibodies	Anti-TNF-α monoclonal antibody, CDP571
Soluble receptors (conjugated to human immunoglobulin)	Soluble IL-1 receptor TNF receptor fusion protein
Immunotoxins	
Antibodies conjugated to toxin	Anti-CD5 conjugated to ricin
Cytokine conjugated to toxin	IL-2 DAB
Immunosuppressive/ regulatory cytokines	IL-10 IL-4
Natural cytokine antagonists	IL-1 receptor antagonist
Small molecule inhibitors inhibiting cytokine release	Metalloproteinase inhibitors
Peptides	Vβ17 peptide vaccination
Immunomodulation	T-cell vaccination Oral tolerance

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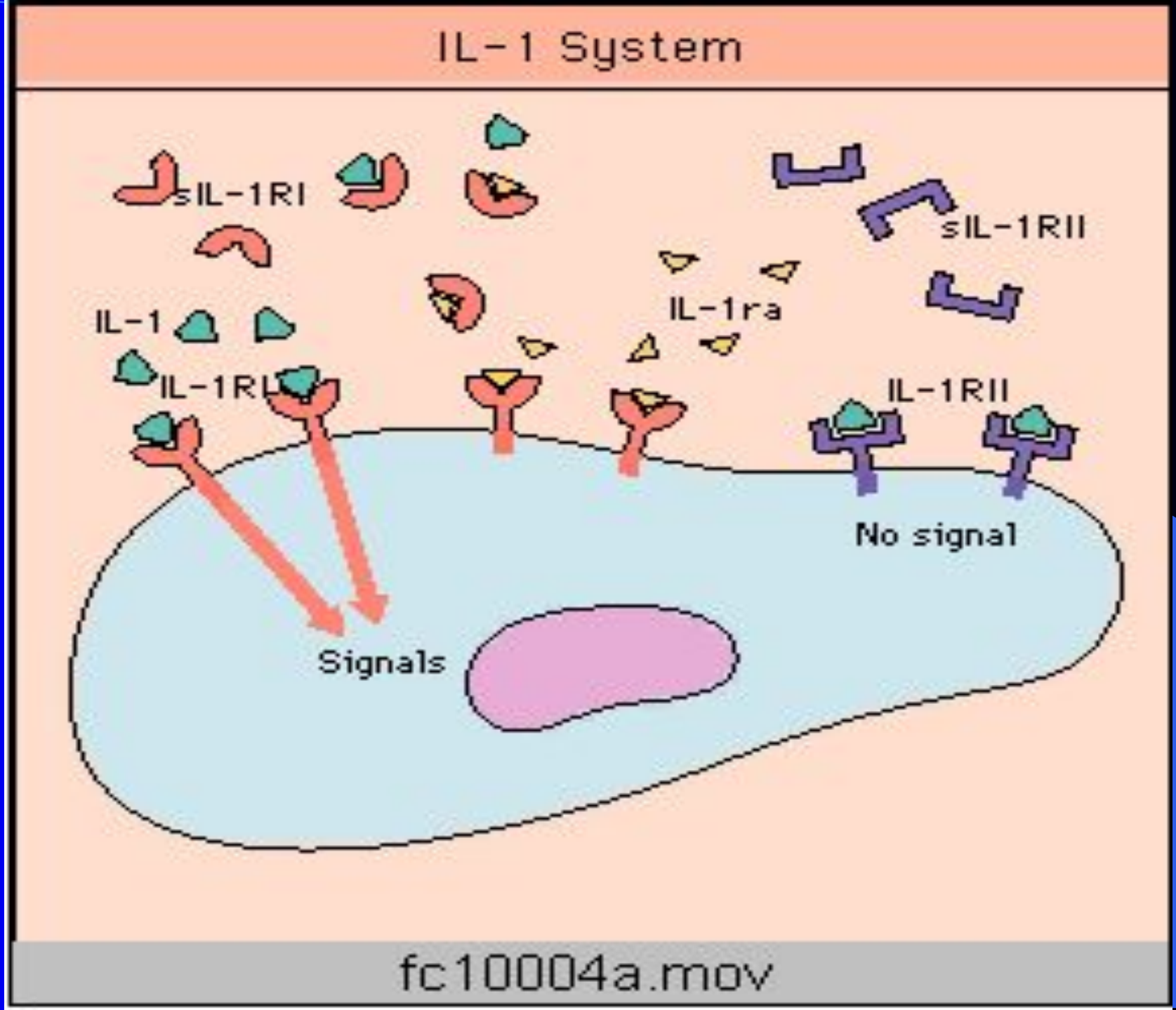
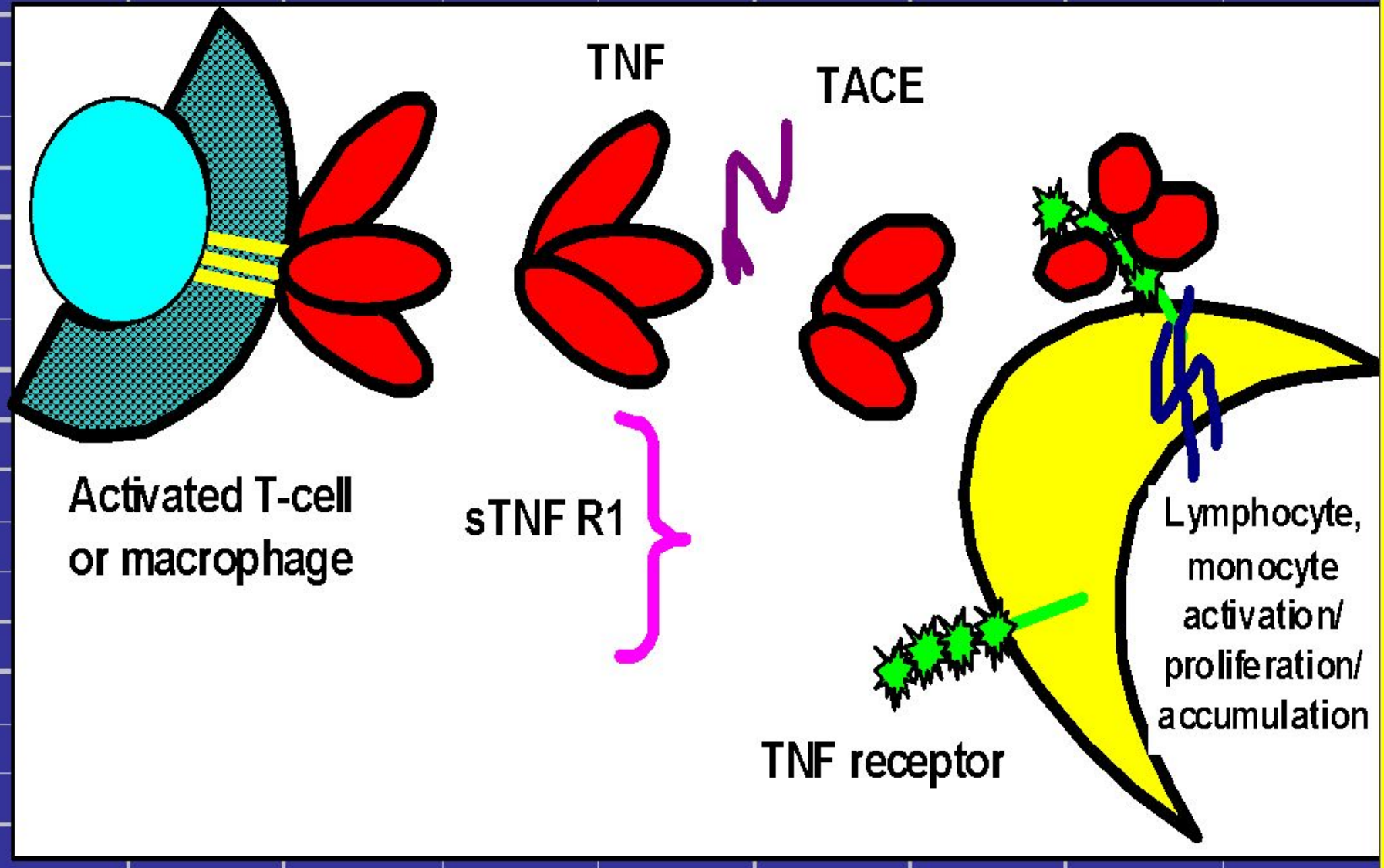

IL-1 System
sIL-1RI
sIL-1RII
IL-1ra
IL-1
IL-1RI
IL-1RII
No signal
Signals
fc10004a.mov

TNF synthesis and action



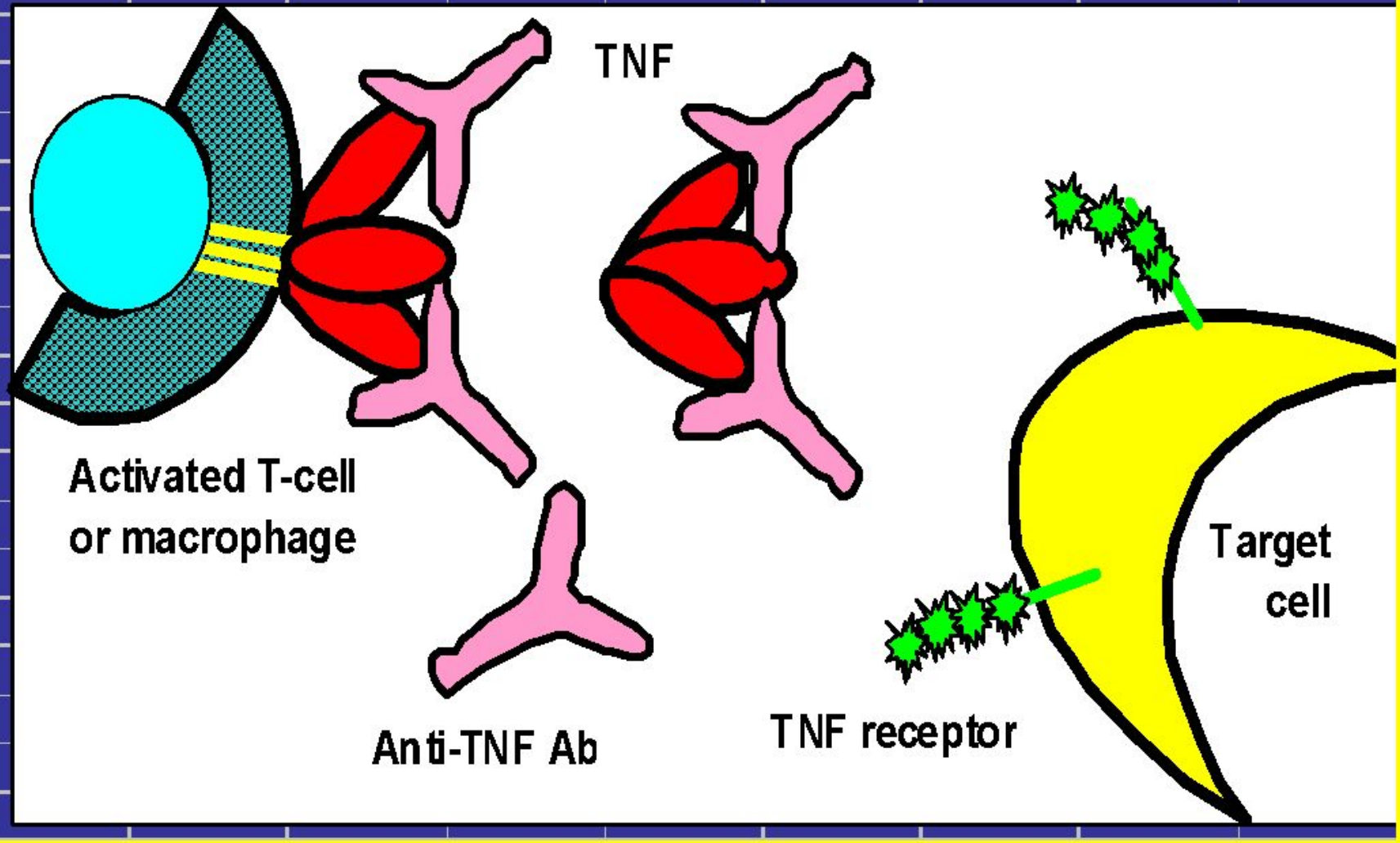
Pro-inflammatory cytokine TNF-alpha

Produced by activated monocytes, macrophages, lymphocytes

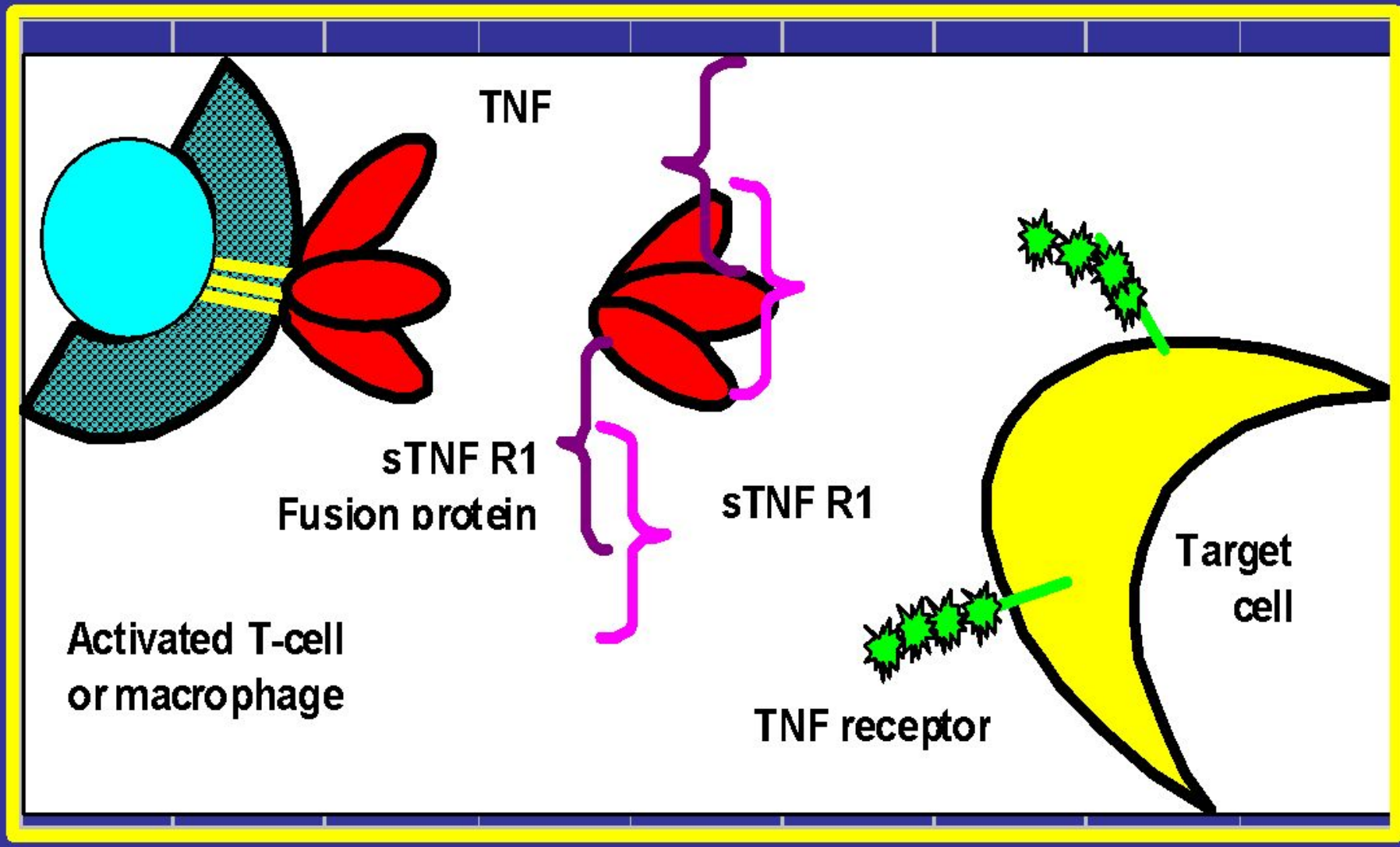
- Fibroblast's activation
- Activation of prostaglandin synthesis
- Induction of adhesion molecules expression
- Induction of RAS (reactive oxygen species)
- Activation of immune system
- Activation of metalloproteinases
- Induction connective tissue breakdown

Central mediator of joint inflammation

Mechanism for antibody neutralization of TNF alpha



Mechanism for TNF alpha blocking by fusion protein



Advantages and Disadvantages of Anticytokine Therapy

Advantage	Disadvantage
Excellent anti-inflammatory targets	Transient effect, therefore long-term treatment necessary
Many targets to choose from	Nonspecific and therefore risk of immunosuppression
Rapidly effective	Many treatments have short half-lives

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Biological therapy and side effects

- **Anti-TNF: Infliximab (Remicade) antibodies to TNF, given intravenous schedule: weeks 0,2,4, and every 8 weeks**
- **hypersensitivity**
- **HACA-neutralizing antibodies, the need for MTX**
- **ANA, Anti-DNA, rare drug induced lupus**
- **very rare hematological malignancy**
- **demyelinating disorder**
- **aplastic anemia**
- **15% patients are not responders**
- **infections, tuberculosis**

Biological therapy and side effects

- Ethanercept (Enbrel) soluble receptor to TNF, given subcutaneously 25 mg twice a week
- Local reactions
- Hypersensitivity
- Non-neutralizing antibodies, non need for MTX
- ANA, Anti DNA, rare drug lupus
- Neuropathy
- Very rare hematological malignancy (case reports)
- infections, rare tuberculosis

Malignancy and TNF-blockage

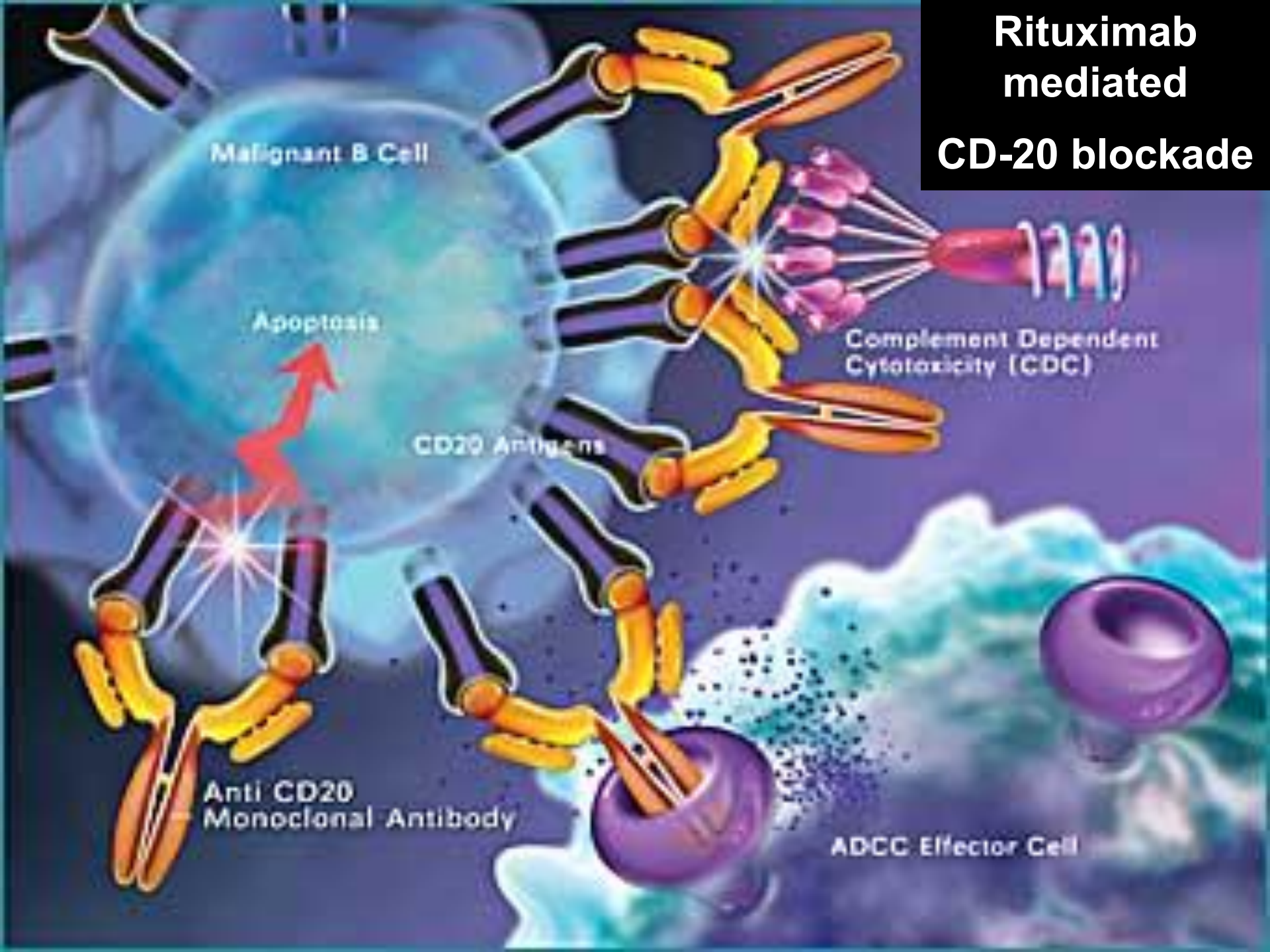
RA itself, MTX itself are associated with high risk of malignancy (Lymphoma) – 2-3 fold

- Infliximab - no evidence for a causal relationship between TNF-a antagonism and the development of lymphoid or nonlymphoid cancers.

Cohen RB, et al. Can J Gastroenterol 2001

- Etanercept – 17 malignancies in 1197 patients during 36 monthes

Beauparlant P, et al. Semin Arthritis Rheum


Rituximab mediated
CD-20 blockade
Malignant B Cell
Apoptosis
CD20 Antigens
Complement Dependent Cytotoxicity (CDC)
Anti CD20 Monoclonal Antibody
ADCC Effector Cell

Humira (Adalimumab) – Anti-TNF fully humanized, 2 week s/c

Simponi (Golalimumab) – Anti-TNF fully humanized, monthly s/c

Actemra (MRA) Anti-IL-6

Kineret Anti-IL1

Canakimumab Anti-IL-1R

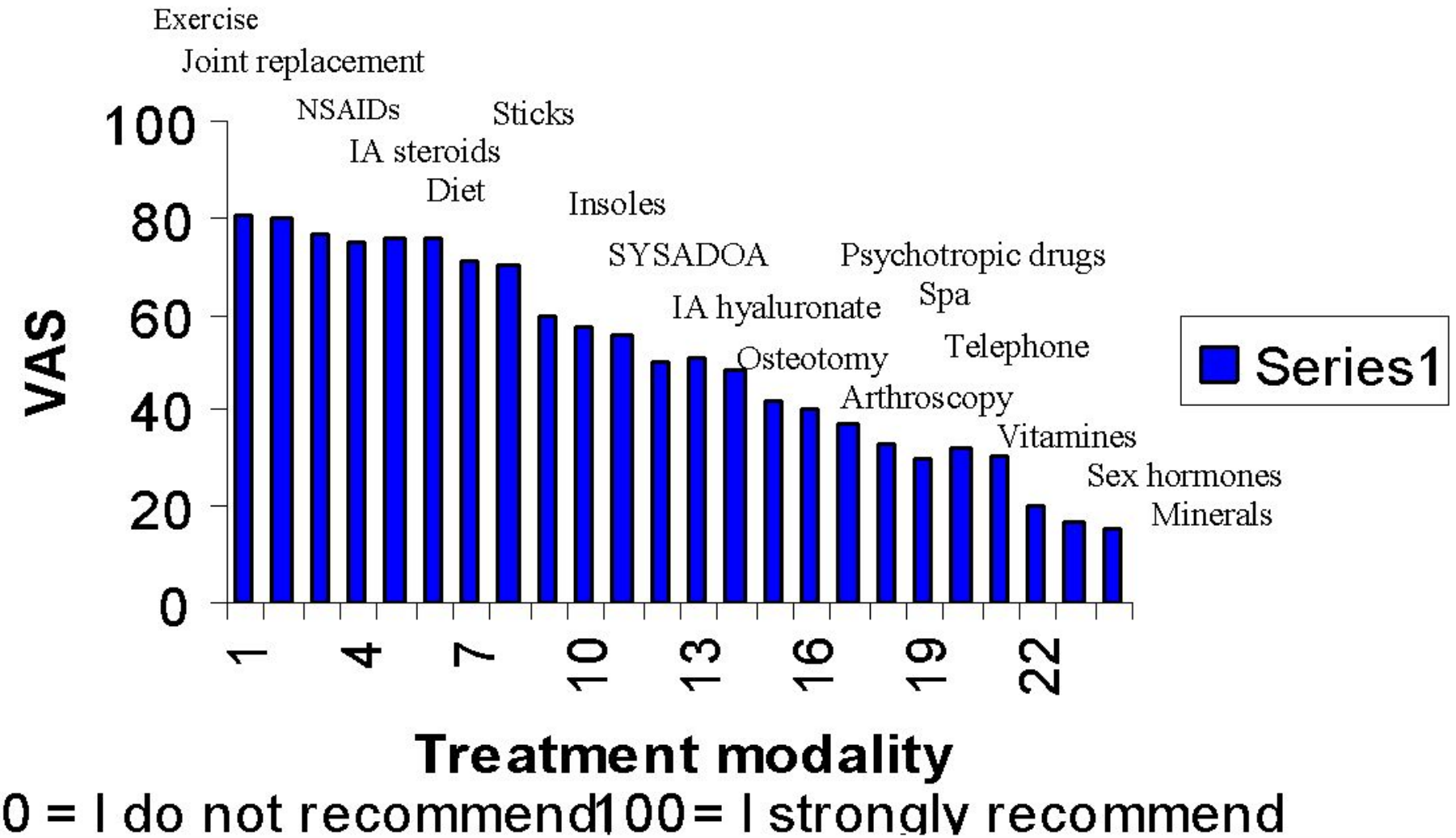
Stelara Anti-IL-17/23

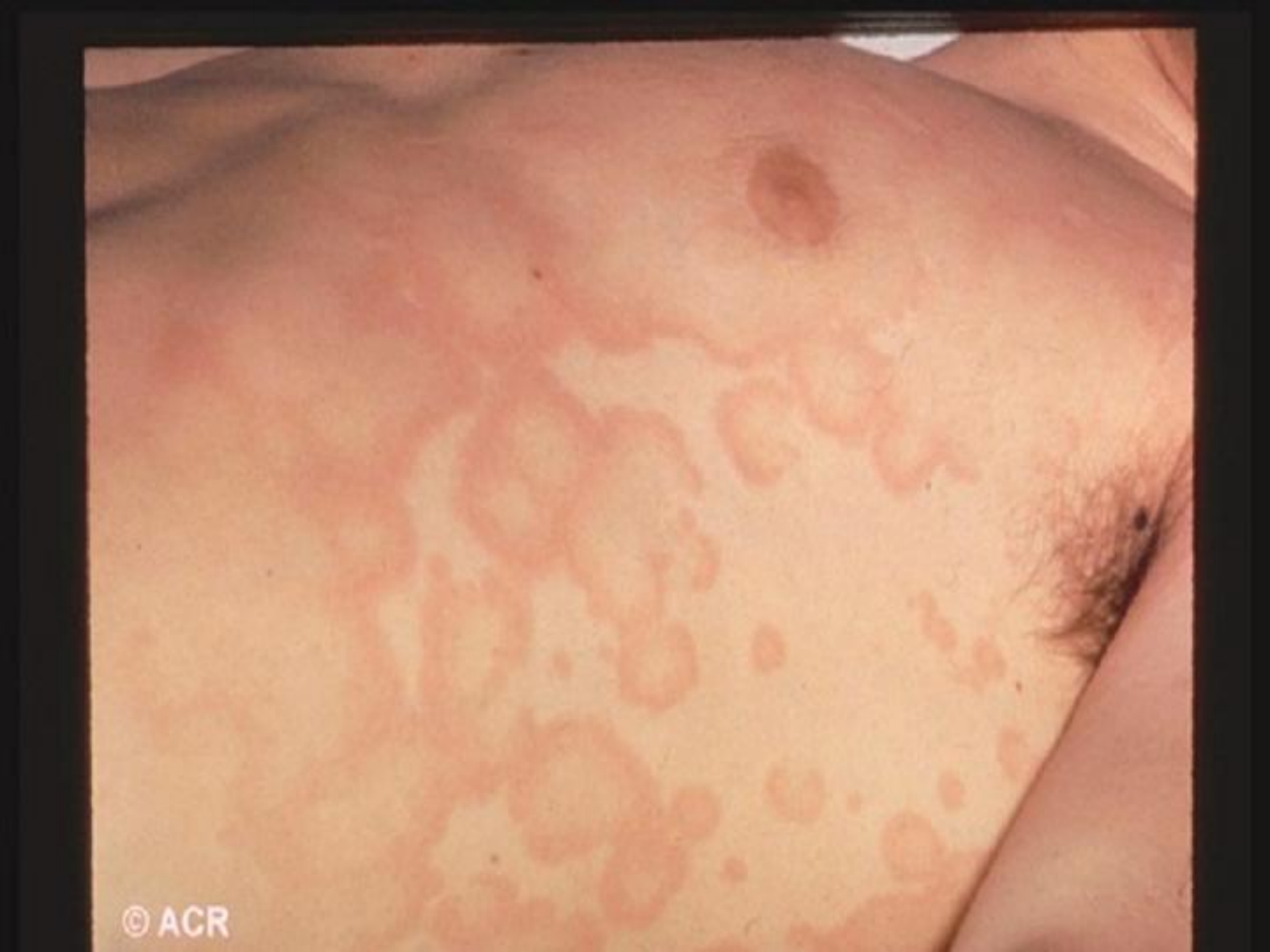
IVIG 125-150g/month

Benlysta (Belymumab) Ab to B-cell activated factor 10mg/kg IV

Orencia (Abatacept) Costimulator inhibitor

Overall experts' opinion of the usefulness of the different treatment modalities for OA (EULAR)

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