Pharmacology - MSS

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Disease Modifying Anti-Rheumatic Drugs (DMARDs)

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These are a group of drugs that are used mainly to treat the condition of a rheumatoid arthritis although many of them are also used for the treatment of other conditions throughout the body.

Rheumatoid arthritis

Rheumatoid arthritis is an immunological disease that have multiple systemic effects it can lead to shortening of life and it reduces the quality of life

- It is associated with :

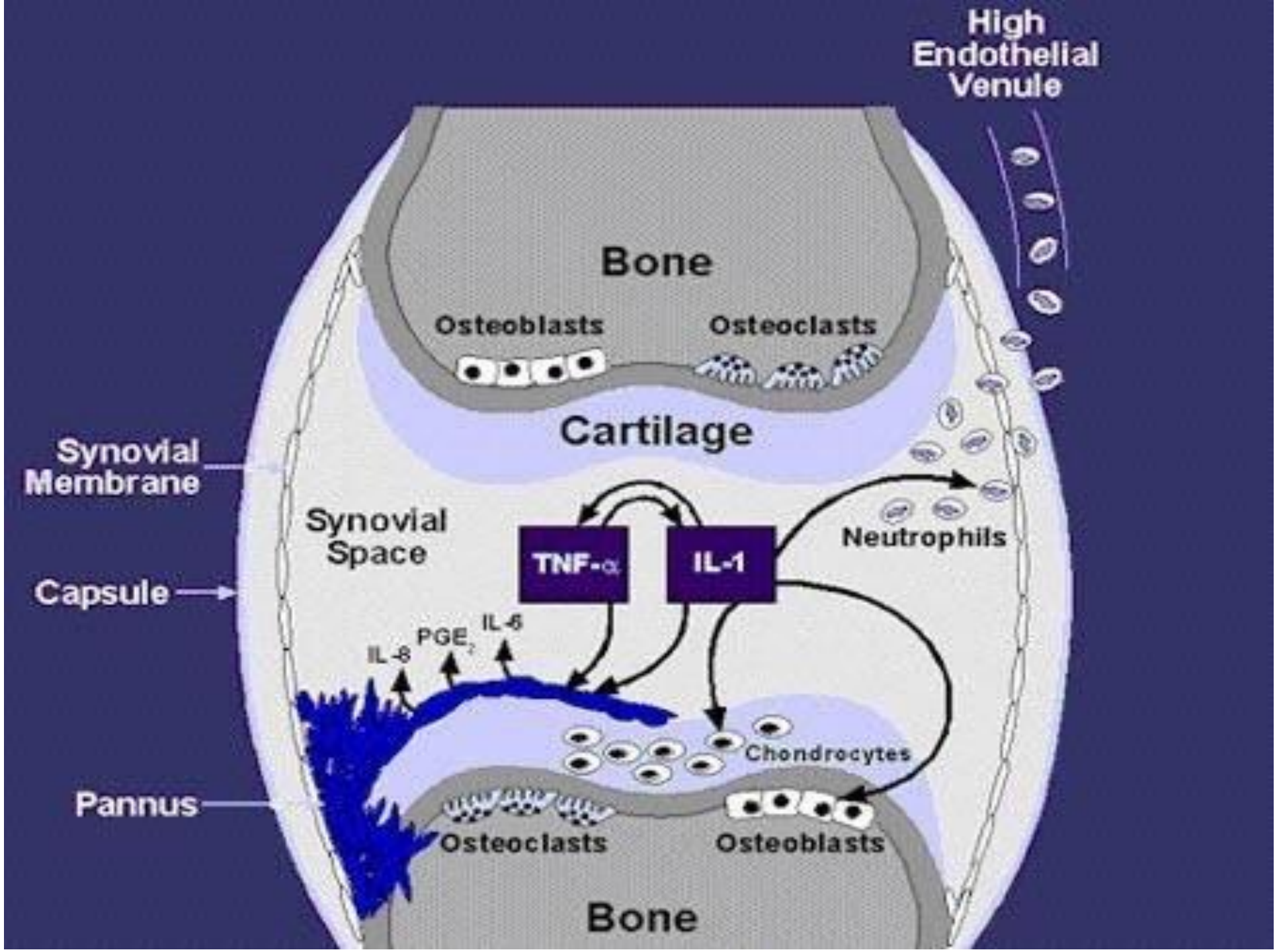
- Chronic synovial inflammation
- Autoimmune

- Cytokine networks are responsible for inflammation & joint destruction

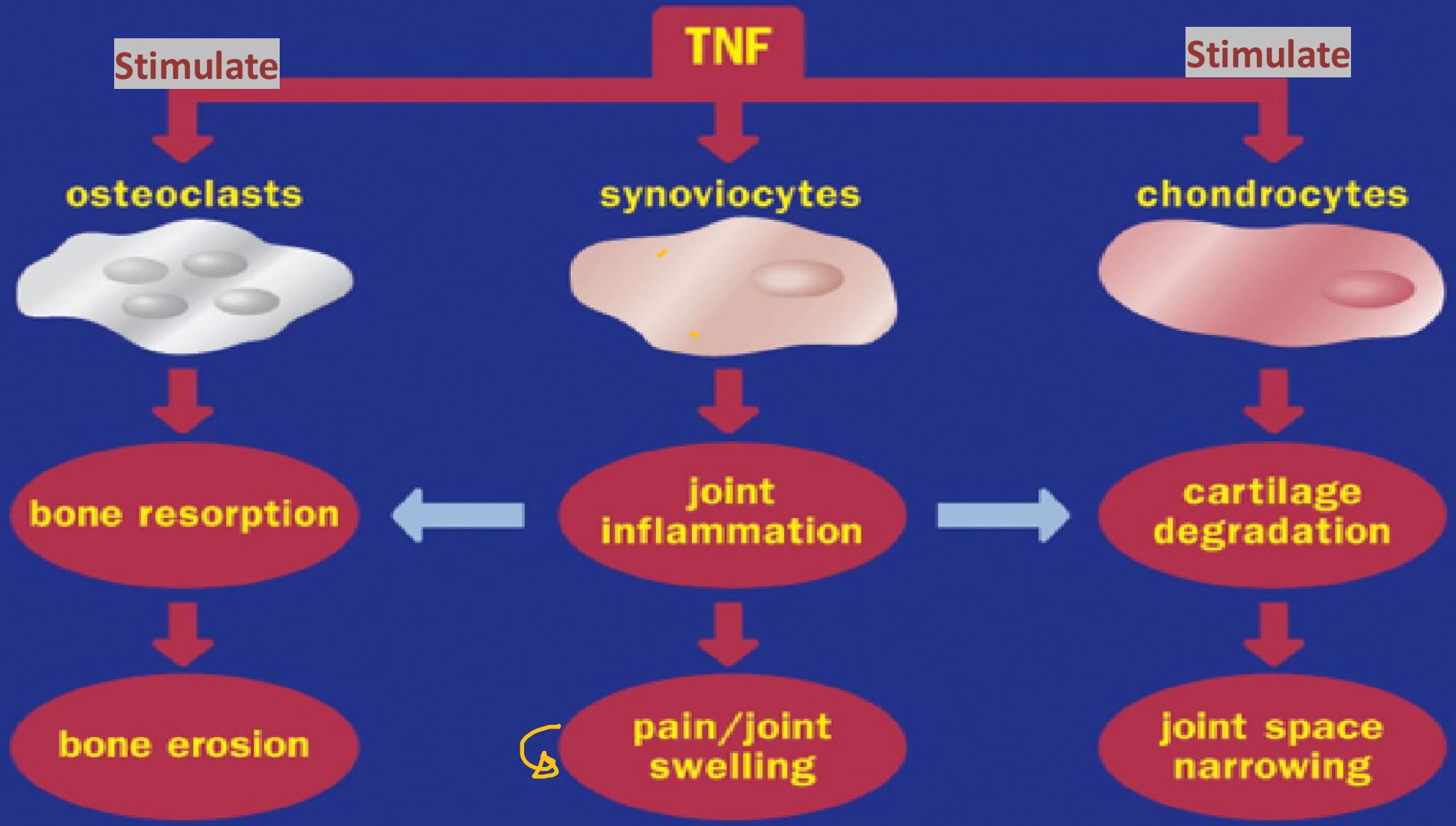
- Tumor Necrosis Factor-α (**TNF-α**)
- **Interleukins - 1,6,17 ,8**
- Prostaglandins

❖ we are going to see a lot of cytokines and chemokines released at synovial spaces , most important of this we have TNF alpha which can Stimulate the production of interleukins such as interleukin -1

Moreover, interleukin -1 can stimulate the production of TNF alpha which further stimulate other cytokines such as IL -8 , prostaglandin and IL-6


High Endothelial Venule
Bone
Osteoblasts
Osteoclasts
Cartilage
Synovial Membrane
Synovial Space
TNF-α
IL-1
Neutrophils
Capsule
IL-8
PGE2
IL-6
Chondrocytes
Pannus
Osteoclasts
Osteoblasts
Bone

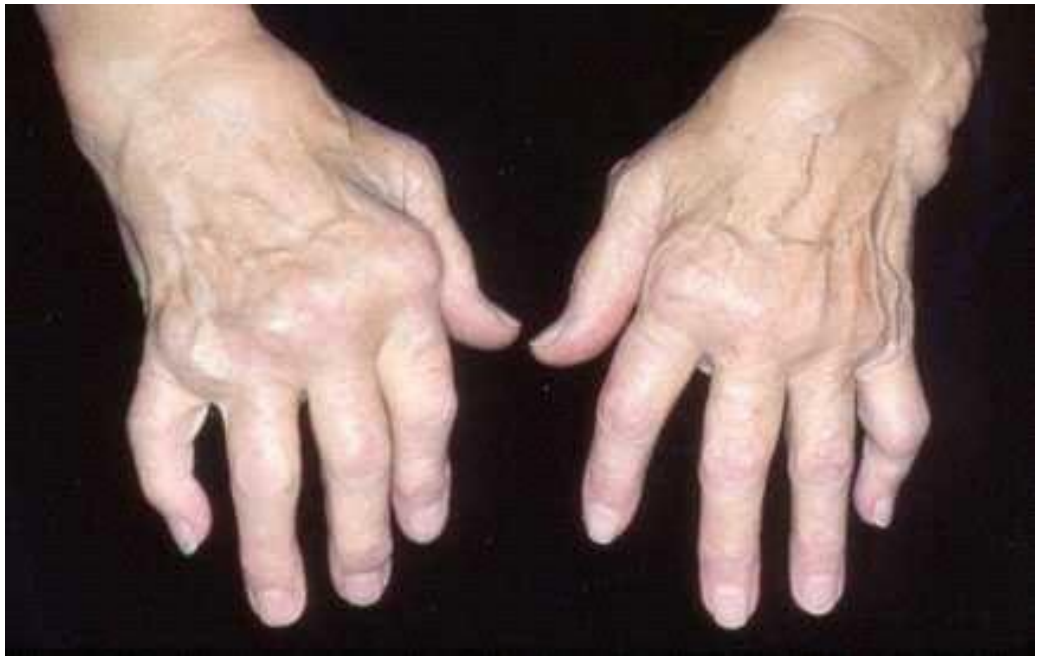
Destructive effects of TNF

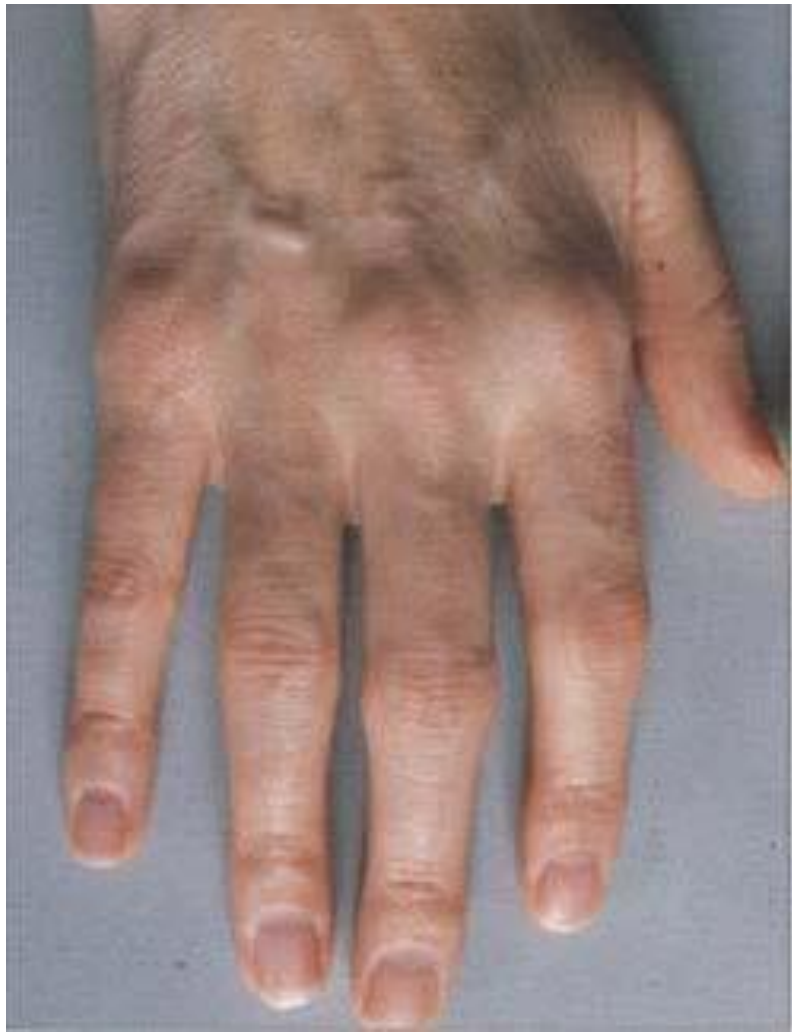


Signs and symptoms of rheumatoid arthritis

Disability in Early RA

- Inflammation
  - Swollen
  - Stiff
  - Sore
  - Warm
- Fatigue
- Potentially Reversible





Drugs for RA

- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Glucocorticoids
- Disease-modifying anti-rheumatic drugs (DMARDs)
  [composed of two general categories]

1. Synthetic
2. Biologic

DMARDs

Disease Modifying

Anti-Rheumatic Drugs

- Reduce swelling & inflammation of **Rheumatism**
- Improve [**relieve**] the pain
- Improve function of the joints

•Have been shown to reduce radiographic progression (erosions)

Synthetic DMARDs

- Methotrexate
- Sulphasalazine
- Chloroquine
- Hydroxychloroquine
- Cyclophosphamide
- Cyclosporin
- Leflunomide
- Mycophenolate Mofetil

The effect of these disease modifying therapies may take 6 weeks or up to 6 months to become clinically evident , as compared to the biological agents we can see clinical improvement with biological agent within 2 weeks or less.

Methotrexate (MTX)

- "**Gold standard**" for DMARD therapy (first line DMARD treatment of RA)
- General Mechanism of action:
  Dihydrofolate reductase inhibitor
- ↓ thymidine & purine nucleotide synthesis but it isn't the main mechanism of action in treating RA
- Absorption variable [slide 14]
- Elimination mainly renal,
- - It is absorbed orally , absorption is variable, but it can reach up to 70% of the oral administrated dose
- - It is usually eliminated through the kidney
- - Half-life of this drugs can be ranging between 6-9 hours

MTX adverse effects

- **Mechanism of action** at the low doses in RA (so it can be used of doses of 7.5 to 35 mg weekly *a lower dose than the dose we use for chemotherapy*)inhibition of aminoimidazolecarboxamide ribonucleotide (AICAR) transformylase and inhibition of thymidylate synthetase.

- Accordingly, AICAR accumulates intracellularly, competitively inhibits AMP deaminase, leading to an accumulation of AMP.
- The AMP is released and converted extracellularly to adenosine, which is a potent inhibitor of inflammation.

Details in the next slide

MOF cont..

- As a result, the inflammatory function of neutrophils, macrophages , dendritic cells and lymphocytes is suppressed.
- In addition to that MTX has a secondary effect of polymorph nuclear chemotaxis which also leads to **inhibit the inflammation.**

- There is some effect on dihydrofolate reductase, and this will affect the lymphocyte and macrophage functions, but it is not the principal mechanism of action of this drug.
- Also, MTX have direct inhibitory effect on proliferation, and it can stimulate apoptosis of immune inflammatory cells , it can also have pro – inflammatory on cytokines that are linked to **rheumatoid synovitis**.

MTX adverse effects

- Hepatotoxicity
- Bone marrow suppression
- Dyspepsia, oral ulcers
- Pneumonitis
- Teratogenicity

- If the patient is given supplementation of **Folic acid** this can reduce GI & BM effects
- Monitoring the different variables (doing routine CBC (complete blood count)checks) to make sure we don't have bone marrow suppression.
- FBC (full blood count), ALT (lever functions test) , Creatinine (Kidney function test)

Sulphasalazine

- Sulphapyridine + 5-aminosalicylic acid (the most active moiety when it used for the treatment of rheumatoid arthritis.)

- These drugs help in removing toxic free radicals from the Body

In addition, it has been noted that in RA patient's **IgA** and **IgM** rheumatic factor are decreased additionally suppression of T-cells responses and inhibition of B-cell proliferation. Thus, reduction in the inflammatory cytokines these include IL- 1,6,12 & TNF alpha.

- Remission in 3-6 month
- Elimination hepatic (liver)
- **Side effects** : **Dyspepsia, rashes, BM suppression**

Chloroquine, Hydroxychloroquine

- Mechanism unknown but it can suppress T-lymphocyte responses to the mitogens.
- Also, it can cause **decrease** leukocyte chemotaxis , stabilization of lysosomal enzymes and inhibition of DNA and RNA synthesis in addition to trapping free radicals or convincing free radicals
- Interference with antigen processing ?
- Anti- inflammatory and immunomodulatory

- Prescribed For mild RA
- Take a month to see the effect

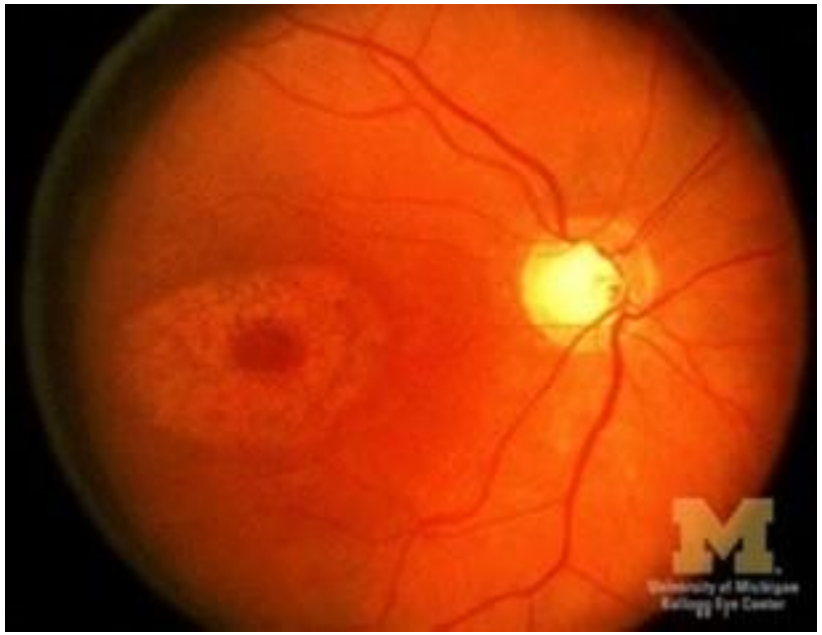
Side effects

Ocular toxicity

- Irreversible Retinal toxicity, corneal deposits
- We have to perform Ophthalmologic evaluation every 6 months

** Some people say that monitoring should be performed every 12 months. However, it's better –depending on the dose to do it every 6 months.

Other side effects include dyspepsia , nausea , vomiting, abdominal pain , rashes and sometimes nightmares.



Leflunomide

- Competitive inhibitor of dihydroorotate dehydrogenase (rate-limiting enzyme in de novo synthesis of pyrimidines)

- Effect :
  - Reduce lymphocyte proliferation (T- cell proliferation and production of auto-antibodies by B- cells
  - IL-10,8 receptor mRNA is decreased
  - TNF-alpha dependent nuclear factor is decreased thus, NF kappa B activation will be reduced.

Leflunomide

- Oral
- T ½ - 4 – 28 days
- Elimination hepatic

- Action in one month
- Avoid pregnancy for 2 years (because it inhabits nucleotide synthesis)

Side effects

- Hepatotoxicity (elevation in lever enzymes)
- BM suppression
- Diarrhea (in 25% of patients)
- Rashes
- In addition to mild alopecia, weight gain and increase in BP.

CYCLOPHOSPHAMIDE

Mechanism of Action

Cyclophosphamide is a synthetic DMARD. Its major active metabolite is phosphoramide mustard, which cross-links DNA to prevent cell replication. It suppresses T-cell and B-cell function by 30–40%; T- cell suppression correlates with clinical response in the rheumatic diseases.

CYCLOPHOSPHAMIDE

Indications

Cyclophosphamide is active against rheumatoid arthritis when given orally at dosages of 2 mg/kg/d but not intravenously.

It is used regularly to treat systemic lupus erythematosus, vasculitis, Wegener's granulomatosis, and other severe rheumatic diseases.

Toxicities

dose-related …… primarily in rapidly growing tissues:
bone marrow, gastrointestinal tract, and reproductive system.

Nausea and **vomiting** **loss of appetite**
or **weight** **abdominal pain, diarrhea** ,
hair loss, sores on the mouth tongue
changes in skin color, changes in color or
growth of **fingernails** or **toenails.**

Cyclosporine

- **Given, orally, IV, by inhalation, or as ophthalmic solution.**
- **Metabolized by cytochrome P450 3A enzyme system with resultant multiple drug interactions and variability in bioavailability, and consequently, there is a need for routine drug monitoring.**

Clarification
because this drug is metabolized by cytochrome P450 any drug given for the patient at the same time can have deleterious effects because some drugs are either inhibitors or activators of p450 So this alters the levels of active form of the drug in the bloodstream

For example
Antifungal agent such as **fluconazole**
It will inhibit the action of metabolizing enzyme which will cause increase in the circulating levels of cyclosporine and increase of its toxicity

Cyclosporine

- Side effects
- Nephrotoxicity.
- Hypertension.
- Hyperglycemia.
- Liver dysfunction.
- Hyperkalemia.
- Altered mental status, seizures.
- Hairsutism.
- Lymphoma and other cancers (Kaposi's sarcoma, skin cancer) due to induction of TGF-ß.

Cyclosporin Monitoring Parameters

- Cyclosporine trough levels.
- Serum electrolytes.
- Renal function.
- Hepatic function.
- Blood pressure.
- Serum cholesterol.

Clinical Uses of Cyclosporine

1. Human organ transplantation,
2. suppression of Graft-versus-host diseases after hematopoietic stem cell transplantation,
3. Selected autoimmune disorders, including uveitis, rheumatoid arthritis, psoriasis, and asthma.

Mycophenolate Mofetil

- Derived from a mold *Penicillium glaucus*.
- Hydrolyzed to mycophenolic acid, the active immunosuppressive moiety.
- Given orally or IV.
- Plasma levels are monitored because it can cause myelosuppression and neutropenia
- Can cause Nausea ,Vomiting , Diarrhea , abdominal pain, headache, hypertension, and reversible myelosuppression, primarily neutropenia.
- It can case hepatotoxicity , thrombocytopenia , anemia and leukopenia
- There is an associated risk of increase of infection and rarely associated with increased malignancy.

MYCOPHENOLATE

- MPA is a reversible inhibitor of the enzyme inosine monophosphate dehydrogenese (IMPDH).
- This leads to depletion of guanosine nucleotides.
- depletion of guanosine nucleotides has anti proliferation effect on lymphocytes (both T and B cells).

MYCOPHENOLATE

- MPA is effective for the treatment of renal disease due to systemic lupus erythematosus and may be useful in vasculitis and Wegener's granulomatosis (sever forms of Rheumatism) .

- Although MMF is occasionally used at a dosage of 2 g/d to treat rheumatoid arthritis, there are no well-controlled data regarding its efficacy in this disease.

Combination therapy (using 2 to 3) DMARDs at a time works better than using a single DMARD

Which will help us to lower the dose of the agents we are using this will decrease the side effects.

Common DMARD Combinations

- **Triple Therapy**
- Methotrexate, Sulfasalazine, Hydroxychloroquine

- **Double Therapy**
- Methotrexate & Leflunomide
- Methotrexate & Sulfasalazine
- Methotrexate & Hydroxychloroquine

BIOLOGIC THERAPY

- Complex protein molecules
- Created using molecular biology methods
- Produced in prokaryotic or eukaryotic cell cultures

These technologies use the hybridoma technology which was started in 1975 and we generate monoclonal antibodies.

remember if we have a humanized monoclonal antibodies so part of this AB comes from the human gene, in this case the name of the drug will end up with U-mab if we have a chimeric that means we have parts of this as coming from another organism such as a mouse in this case the name of the drug ends up with I-mab or Xi-mab

BIOLOGIC THERAPY

Monoclonal Antibodies to TNF

- Infliximab
- Adalimumab

Soluble Receptor Decoy for TNF

- Etanercept

Receptor Antagonist to IL-1

- Anakinra

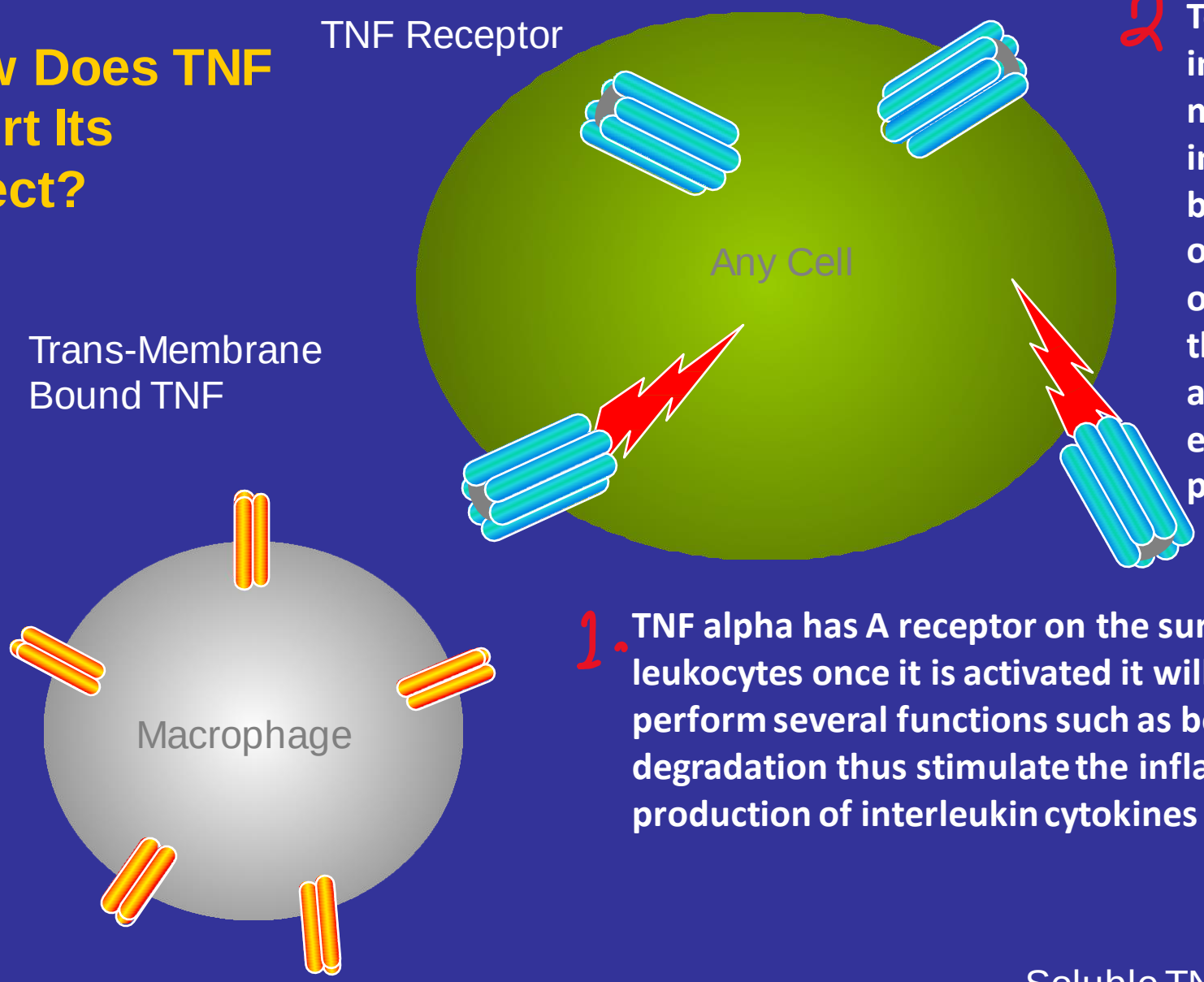
Monoclonal Antibody to CD-20

- Rituximab

Tumour Necrosis Factor (TNF)

- TNF is a potent inflammatory cytokine
- TNF is produced mainly by macrophages and monocytes
- TNF is a major contributor to the inflammatory and destructive changes that occur in RA
- Blockade of TNF results in a reduction in a number of other pro-inflammatory cytokines (IL-1, IL-6, & IL-8)

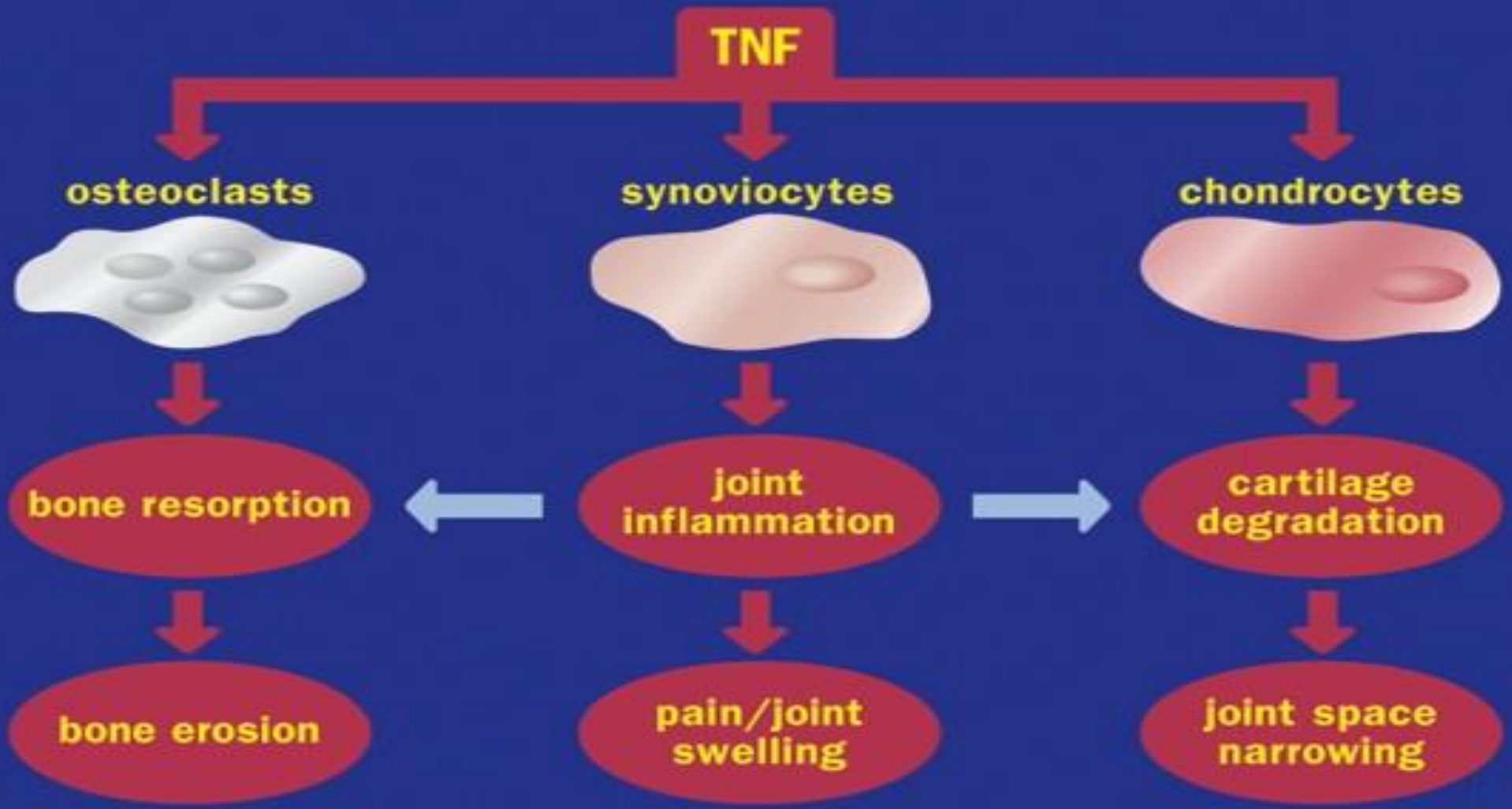
How Does TNF Exert Its Effect?



2 To stop the Propagation of inflammatory process is Using a monoclonal antibody such as infliximab and the antibody can bind to the receptor of TNF alpha on the surface of several cells preventing the activation of the leukocyte and preventing the cascade of event that would lead to the propagation of inflammation.

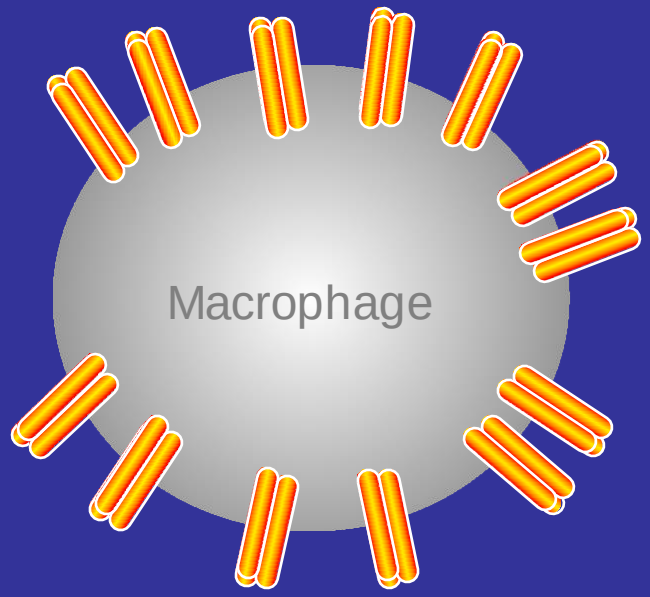
1. TNF alpha has A receptor on the surface of the different leukocytes once it is activated it will cause their activation to perform several functions such as bone resorption & cartilage degradation thus stimulate the inflammatory process by production of interleukin cytokines prostaglandins.

Destructive effects of TNF

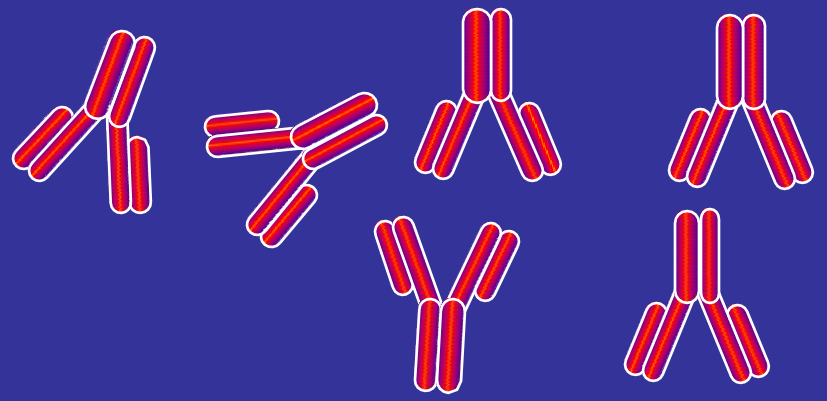


Strategies for Reducing Effects of TNF

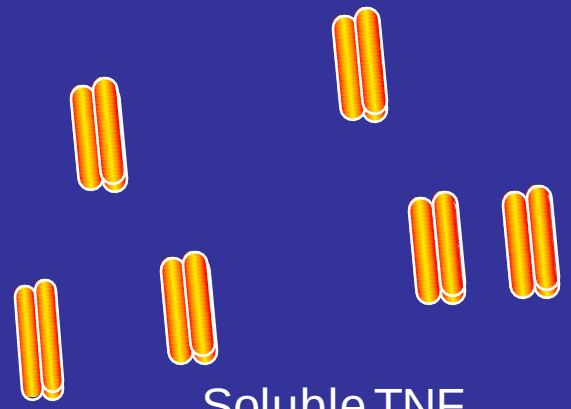
Trans-Membrane Bound TNF



Monoclonal Antibody (Infliximab & Adalimumab)



An example of a soluble recombinant protein, is a recombinant fusion protein called Etanercept which is consisting of two soluble TNF alpha, p75 receptor that are linked to the fc portion of a human IG1.



Soluble TNF

Side Effects

- Infection because they are immunosuppressant
  - –Common (Bacterial)
  - –Opportunistic (Tb)
- Demyelinating Disorders (causing neurological problems)
- Malignancy tumor formation
- Worsening CHF (congestive heart failure)

ABATACEPT

A modified antibody , fusion protein .

MOA: it contains the endogenous ligand CTLA-4 that binds to CD80 and 86, thereby inhibiting the binding to CD28 and preventing the activation of T cells.

Usually the normal process after T-cell has engaged in an antigen presenting cells we have a signal produced by CD-28 on the T-cells and this CD28 will interact with CD-80 and CD-86 on the antigen presenting cells leading to T-cell activation.

Indications

Abatacept can be used as monotherapy or in combination with other DMARDs in patients with moderate to severe rheumatoid arthritis who have had an inadequate response to other DMARDs.

Adverse effects

- There is a slightly increased risk of infection (predominantly of the upper respiratory tract.

- Concomitant use with TNF-α antagonists is not recommended due to the increased incidence of serious infection.
- Infusion-related reactions and hypersensitivity reactions, including anaphylaxis.

- There is a possible increase in lymphomas.