DISEASE MODIFYING ANTIRHEUMATOID DRUGS (DMARDS)

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Objectives

1. Disease modifying anti-rheumatoid drugs (DMARDs) such as methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, D-penicillamine and gold salts.

2. Mechanism of action and profile of adverse effects of these drugs with NSAIDS.

3. Brief discussion about biologic therapy in rheumatoid arthritis, e.g. anti-TNF-α drugs such as etanercept, infliximab, and adalmumab.
4. Other drugs such as interleukin antagonists such as anakinra, are also briefly discussed.

Rheumatoid arthritis

- Chronic synovial inflammation
- Small joints : hands
- 70% females
- Symmetrical
- Autoimmune
- Cytokine networks are responsible for inflammation & joint destruction
  - Tumor Necrosis Factor-α (TNF-α)
  - Interleukins - 1,6,17

PATHOGENESIS

ACPAs (in patient blood even before manifestations) & Citrullinated antigens form immune complexes which stimulate the inflammatory process.

Continuous production of such immune complexes ultimately results in the chronic inflammation, characteristic for RA.

Drugs used in treatment of rheumatoid arthritis:

- Most experts begin DMARD therapy with one of the traditional drugs, such as methotrexate or hydroxychloroquine.

- Inadequate response to the traditional agents may be followed by use of newer DMARDs, such as leflunomide, anakinra, and TNF-inhibitors eg: adalimumab, etanercept, and infliximab.

- In patients who do not respond to combination therapy with methotrexate plus TNF inhibitors, or other combinations, treatment with rituximab or abatacept may be tried.

- Most of these agents are contraindicated for use in pregnant women, breast feeding, liver disease, active infection, leucopenia and peptic ulcer.

Drugs for RA

- Nonsteroidal anti-inflammatory drugs (NSAIDs) (symptomatic)

- Disease-modifying anti-rheumatic drugs (DMARDs)
  - Synthetic
  - Biologic
  - Cortecosteroids (symptomatic)

NSAIDs

- Non-selective COX inhibitors
  - Ibuprofen
  - Diclofenac sodium
  - Add protective treatment for peptic ulcer
- COX–2 inhibitors
  - celecoxib

COX-2 Inhibitors

- COX-2 inhibitors appear to be as effective NSAIDs
- Associated with less GI toxicity
- However increased risk of CV events

90% of the joints involved in RA are affected within the first year

SO TREAT IT EARLY

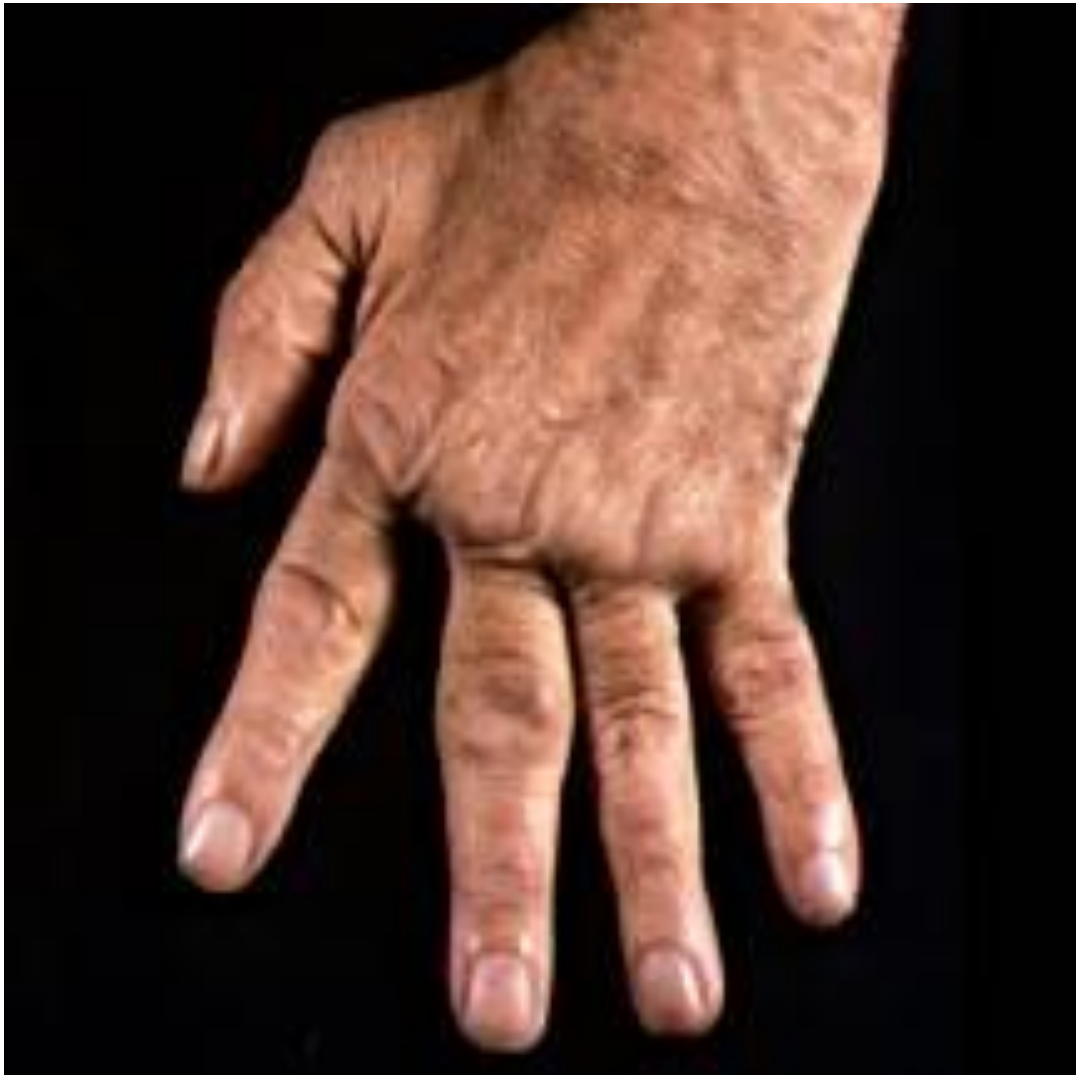
- **Effects of (DMARDs) a in the treatment of RA :**
- 1- Slow the course of the disease
- 2-Induce remission
- 3- Prevent further destruction of the joints and involved tissues.

- Therapy with DMARDs is initiated rapidly to help stop the progression of the disease at the earlier stages.

- Additionally NSAIDs, low-dose corticosteroids, physical therapy, and occupational therapy.

Disability in Late RA (Too Late)

- Damage
  - Bones
  - Cartilage
  - Ligaments and other structures
- Fatigue
- Not Reversible



DMARDs

Disease Modifying Anti-Rheumatic Drugs

- Reduce swelling & inflammation
- Improve pain
- Improve function
- Have been shown to reduce radiographic progression (erosions)

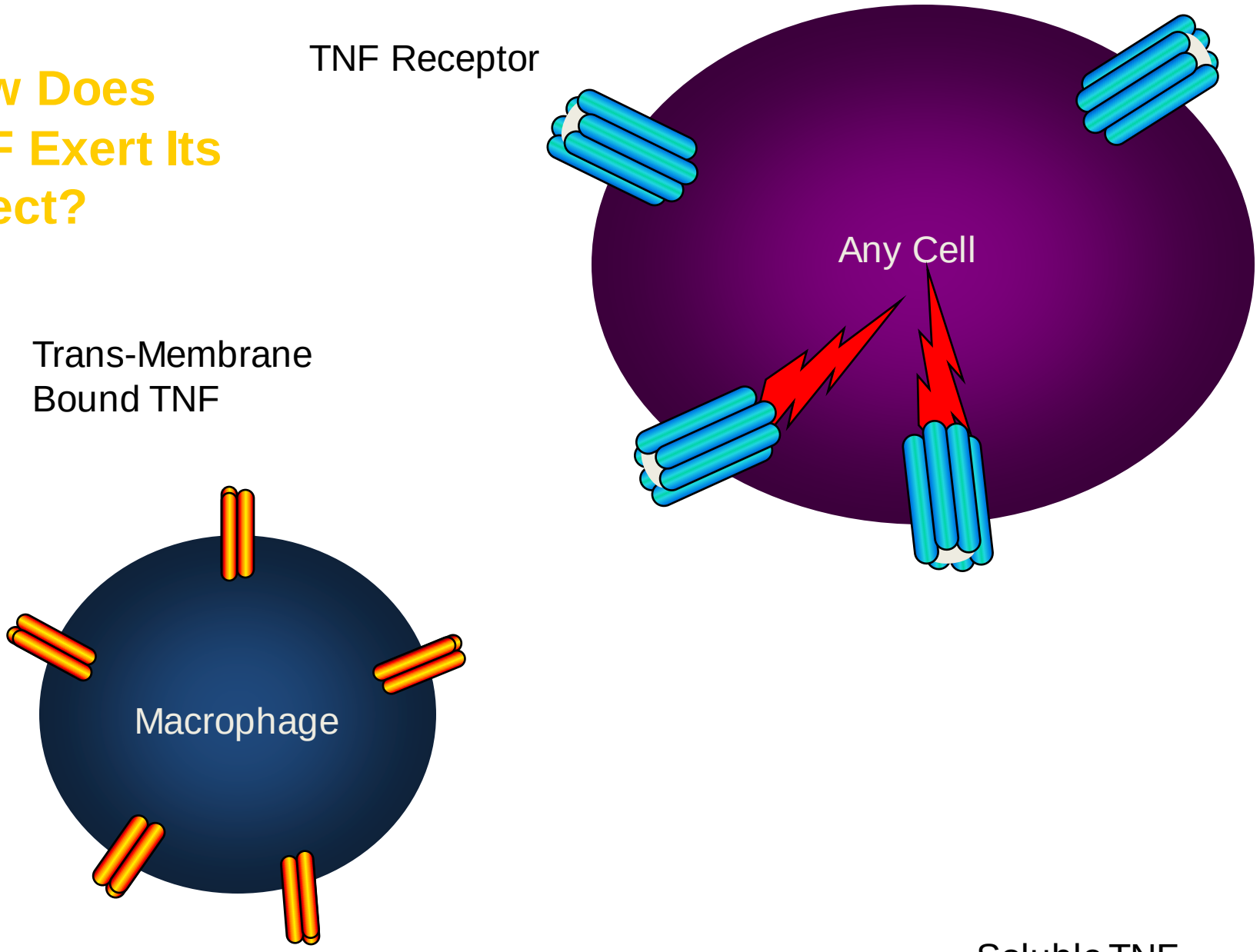
DMARDs

- Synthetic
- Biologic

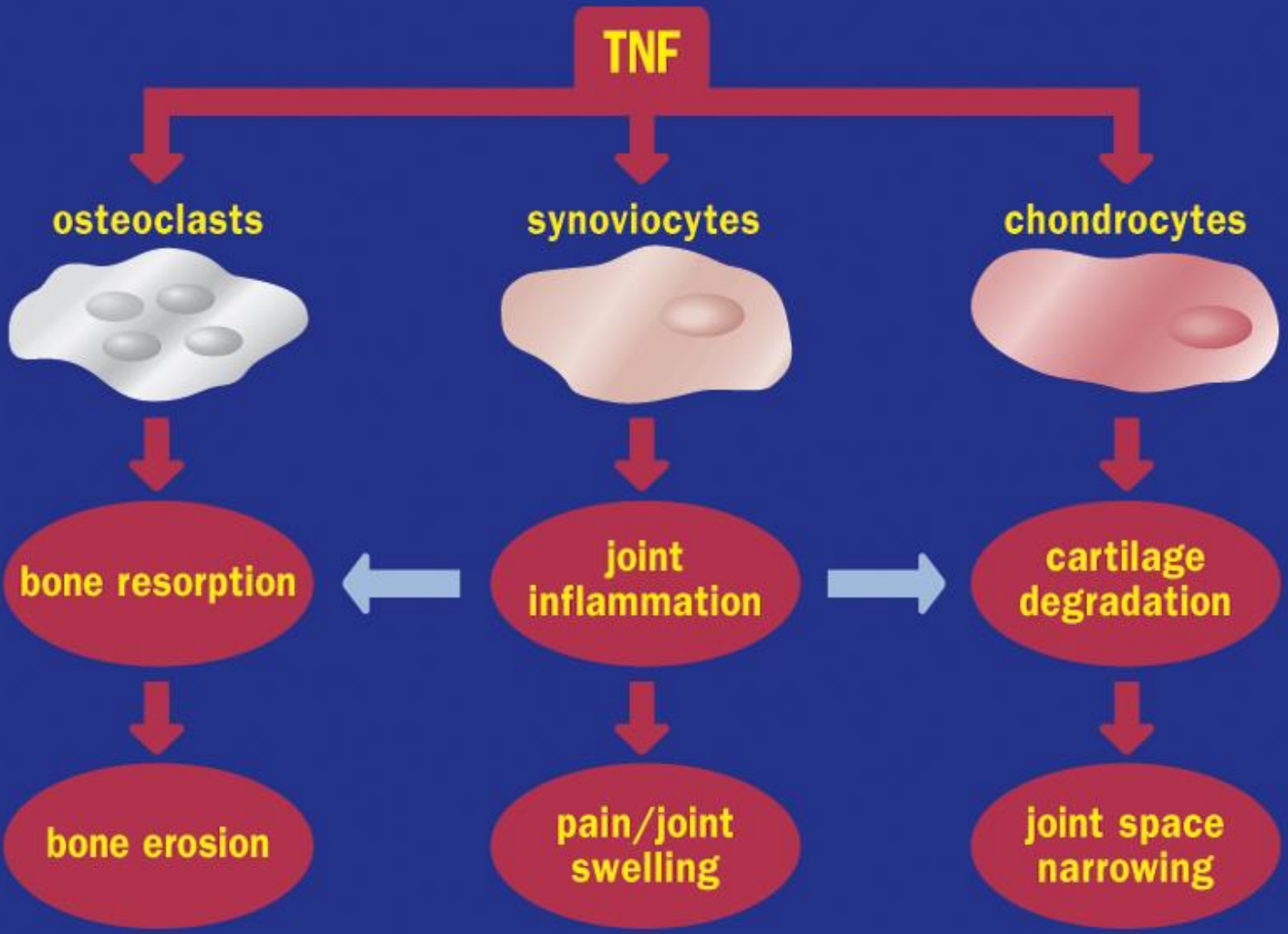
Synthetic DMARDs

- Methotrexate
- Sulphasalazine
- Hydroxychloroquine, chloroquine
- Leflunomide
- Gold salts

How Does TNF Exert Its Effect?

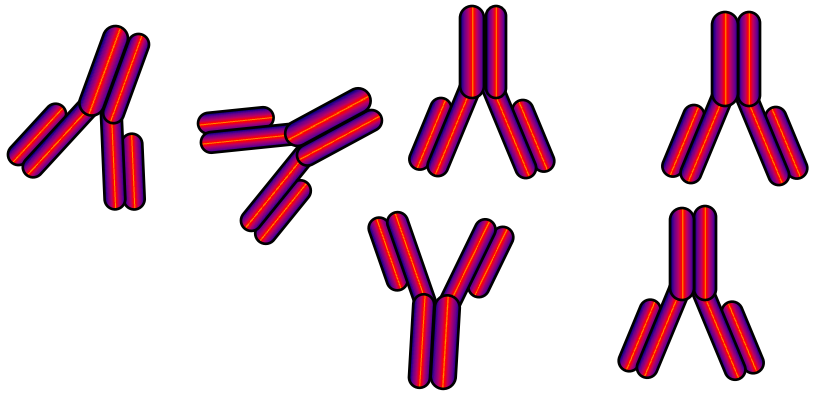


Destructive effects of TNF

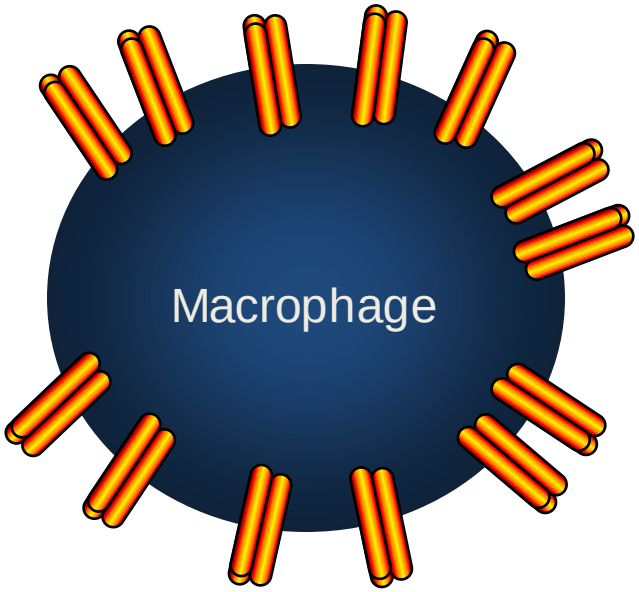


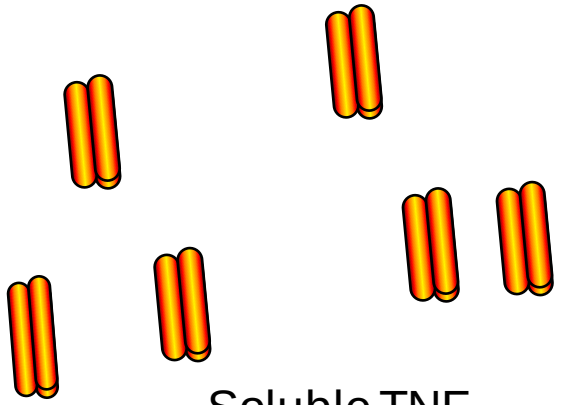
Strategies for Reducing Effects of TNF

Monoclonal Antibody (Infliximab & Adalimumab)



Trans-Membrane Bound TNF





Soluble TNF

Biologic response modifiers (BRMs):

1.TNF α inhibitors: **Etanercept**: **TNF α receptor blocker**

Infliximab Adalimumab (monoclonal antibodies)

Advantages: 1- very effective 2- delay disease progression

Disadvantages: 1- very expensive, so try conventional therapy first 2- contraindicated in patients with history of tumors esp. leukemia, viral hepatitis, immuncomprmised patients

2. IL-1 antagonist: **Anakinra**: short acting given daily and sc injection (disadvantage)

Adjuvant drugs:

Corticosteroids: Prednisolone **5-10 mg** supplement once used in a chronic manner it is difficult to withdraw steroids – exacerbation is precipitated and the patient becomes steroid dependent.

Methotrexate: (immunosuppressant and cytotoxic)

- Used in sever rheumatoid or psoriatic arthritis.
- It is an immunosuppressant, and this may account for its effectiveness in arthritis (60% of patients), an autoimmune disease.
- Response to methotrexate occurs sooner than is usual for other slow-acting agents often within 3-6 weeks of starting treatment.
- **Mechanism of action**: methotrexate is folic acid analogue also inhibits dihydrofolate reductase (DHFR), decresing synthesis of tetrahyrofolate (THF) and it inhibits formation of thymidine residues.
- Methotrexate dose : one tab. Weekly then after 24-48: folic acid therapy

Adverse effects:

- The most common side effects: mucosal ulceration and nausea.
- Cytopenias :bone marrow depression (particularly depression of the WBC count)
- Hepatotoxicity
- acute pneumonia-like syndrome in chronic use

Leflunomide:

- **effective as methotrexate**

- Immunomodulatory and immunosuppressive agent : inhibition of pyrimidine synthesis: inhibiting DNA synthesis in immune cells

- Leflunomide can be used in monotherapy as an alternative to methotrexate or as an addition to methotrexate in combination therapy.

Hydroxychloroquine: (antimalarial drug)

Mechanism of action :

1- inhibition of RNA and DNA synthesis in immune cells

2- stabilization of lysosomal membranes

- It may cause renal toxicity.
- Retinal damage and corneal opacity this is less common and reversible in case of hydroxychloroquine which is preferred over chloroquine

- This drug is employed in the milder nonerrosive disease especially when only one or a few joints are involved or it can be combined with Mtx / sulfasalazine.

Sulfasalazine:

- Sulfasalazine (SSZ) is a prodrug composed of 5-aminosalicylic acid (5-ASA) (immunosupressant) linked to sulfapyridine (antibacterial)
- Sulfasalazine is also used for early, mild RA in combination with hydroxycholoroquine and methotrexate.
- **Side effects** are few but **neutropenia/ thrombocytophenia** occurs in about 10% patients and **hepatitis** is possible.
- It is used as a second line drug for milder cases.

Gold

- Gold is considered to be the **most effective agent** for arresting the rheumatoid process and preventing involvement of additional joints. it was the standard DMARD before the advent of low dose Mtx regimen.

- **Mechanism of action**: It reduces chemotaxis, phagocytosis, macrophage and lysosomal activity : decreasing release of cytokines
- It has no role in late cases

- Gold is heavily bound to plasma and tissue proteins especially in kidney: renal toxicity, Dermatitis and stomatitis, Bone marrow depression

  stays in the body for years.

- Currently available -- gold sodium thiomalate : 50 mg/month.

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

Common DMARD Combinations

- Triple Therapy
  - Methotrexate, Sulfasalazine, Hydroxychloroquine
- Double Therapy
  - Methotrexate & Leflunomide
  - Methotrexate & Sulfasalazine
  - Methotrexate & Hydroxychloroquine

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THANK YOU