ALL INDIA FOOTBALL FEDERATION

TARGET ORTHO

Rheumatoid Arthritis- PART 2

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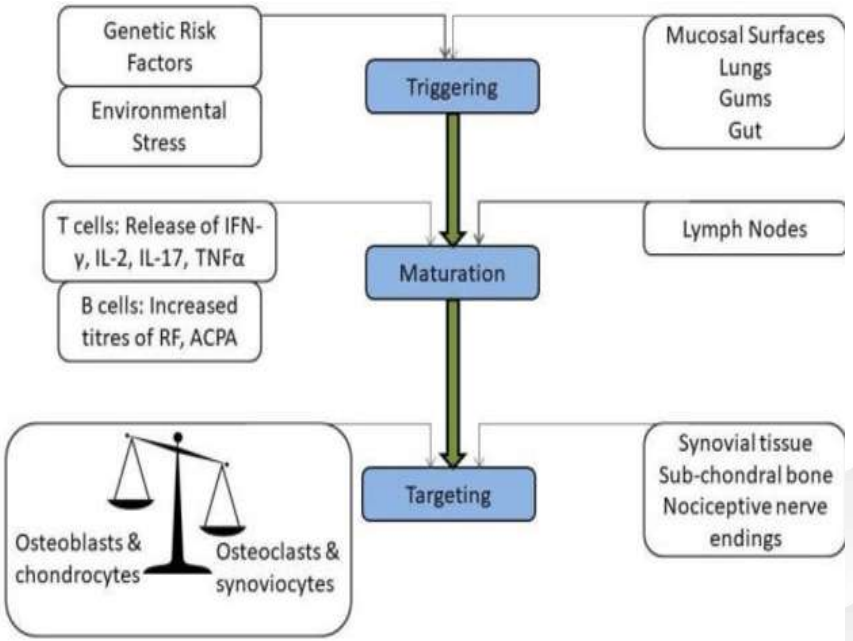
STAGES OF RHEUMATOID ARTHRITIS

TRIGGERING STAGE



RA can be triggered in the potential trigger sites (lung, oral, gut, et al.) by the interaction between the genes and environmental factors.

Onset of self-protein citrullination resulting in the production of autoantibodies against citrullinated peptides.

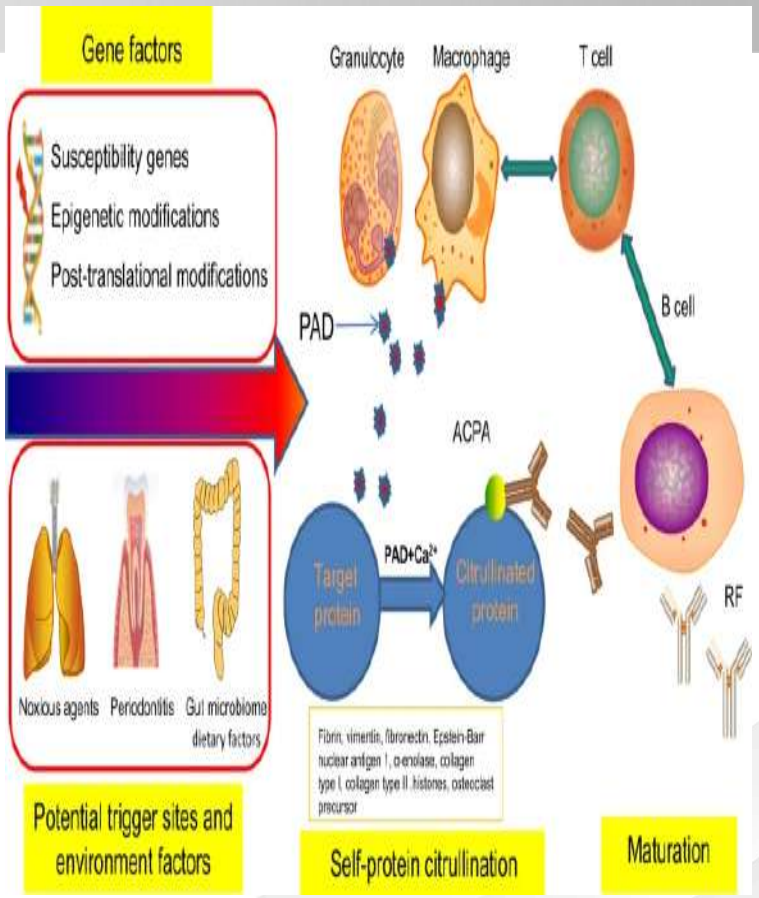
Lung exposure to noxious agents, infectious agents (Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, and Epstein-Barr virus), gut microbiome, and dietary factors may induce the self-protein citrullination and maturation of ACPA.

Citrullination is catalyzed by the calcium-dependent enzyme PAD, changing a positively charged arginine to a polar but neutral citrulline as the result of a post-translational modification.

In RA, PAD can be secreted by the granulocyte and macrophage.

ACPA occurs as a result of an abnormal antibody response to a range of citrullinated proteins, including fibrin, vimentin, fibronectin, Epstein-Barr Nuclear Antigen 1, α-enolase, type II collagen, and histones, all of which are distributed throughout the whole body.

Neoantigens would activate MHC class II-dependent T cells that in turn would help B cells produce more ACPA. The stage is also called loss of tolerance.

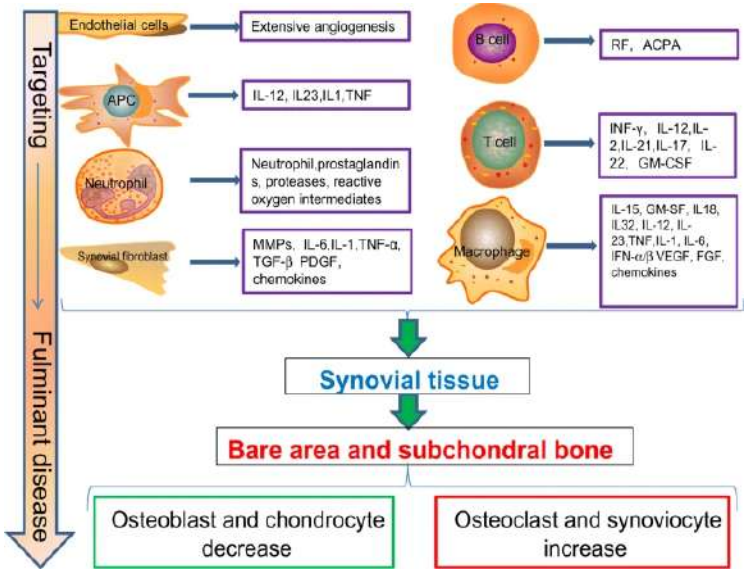


Maturation stage

- This stage is initiated at the site of secondary lymphoid tissues or bone marrow.
- Epitope spreading and a gradually increased titer of ACPA
- Epitope spreading refers to the development of immune responses to endogenous epitopes resulting from the release of self-antigens.
- Production of ACPA reflects break of immunological tolerance. As a result, many citrullination neoantigens would activate MHC class II-dependent T cells that in turn would help B cells produce more ACPA.
- ACPA can induce pain, bone loss, and inflammation in RA.
- RA-specific autoantigens N-acetylglucosamine-6-sulfatase (GNS) and filamin A (FLNA) correlate microbial immunity with autoimmune responses in the joint.

Targeting stage

- The synovial compartment is infiltrated by leukocytes and the synovial fluid is inundated with pro-inflammatory mediators that are produced to induce an inflammatory cascade, which is characterized by interactions of fibroblast-like synoviocytes with the cells of the innate immune system, including monocytes, macrophages, mast cells, dendritic cells as well as cells of adaptive immune system such as T cells and B cells.
- Endothelial cells contribute to the extensive angiogenesis.



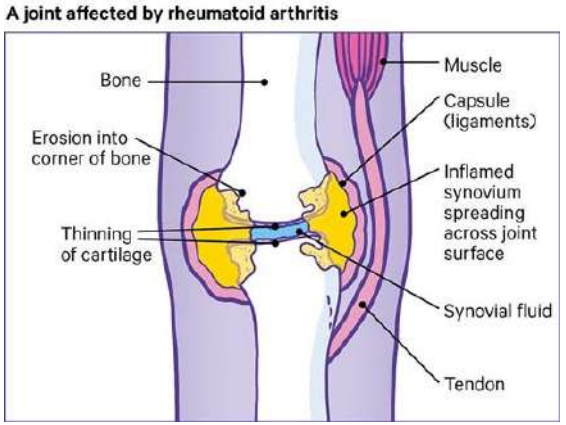
- Bone resorption virtually creates bone erosions, usually found at spots where the synovial membrane inserts into the periosteum, known as a bare area.

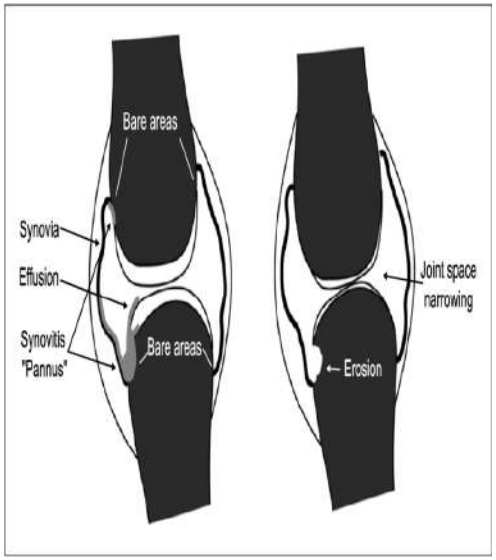
- Destruction of the subchondral bone as the result of a decrease in osteoblasts and an increase in osteoclasts and synoviocytes result in the degeneration of the articular cartilage

Cartilage damage

- The hyperplastic synovium causes major damage to the cartilage via directed adhesion and invasion.
- Mediators of cartilage damage :

- MMPs: Synthesized by FLS and can promote disassembly of the type II collagen network causing biomechanical dysfunction.
- Disintegrin-like metalloprotease with thrombospondin type 1 motifs 4 and 5 and Cathepsins.
- Membrane-type I MMP the predominant proteinase that degrades the collagenous cartilage matrix.
- Under the influence of synovial cytokines, particularly IL-1 and 17A, and reactive nitrogen intermediates[RNI], the cartilage is progressively deprived of chondrocytes that undergo apoptosis(with articular cartilage does not having enough regenerative potential by itself.).
- This results in cartilage degradation demonstrable as joint-space narrowing on radiography.





Fulminant stage

- The fulminant stage contains Hyperplastic synovium, Cartilage damage, Bone erosion, and Systemic consequence.
- Synovium is characterized by a mixture of bone marrow-derived macrophages and specialized FLSs(FIBROBLAST LIKE SYNOVIOCYTES).
- CAUSE:

1. Abnormal proliferation of FLS results from a loss of contact inhibition by producing inflammatory cytokines and proteinases, such as matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) that perpetuate joint destruction.

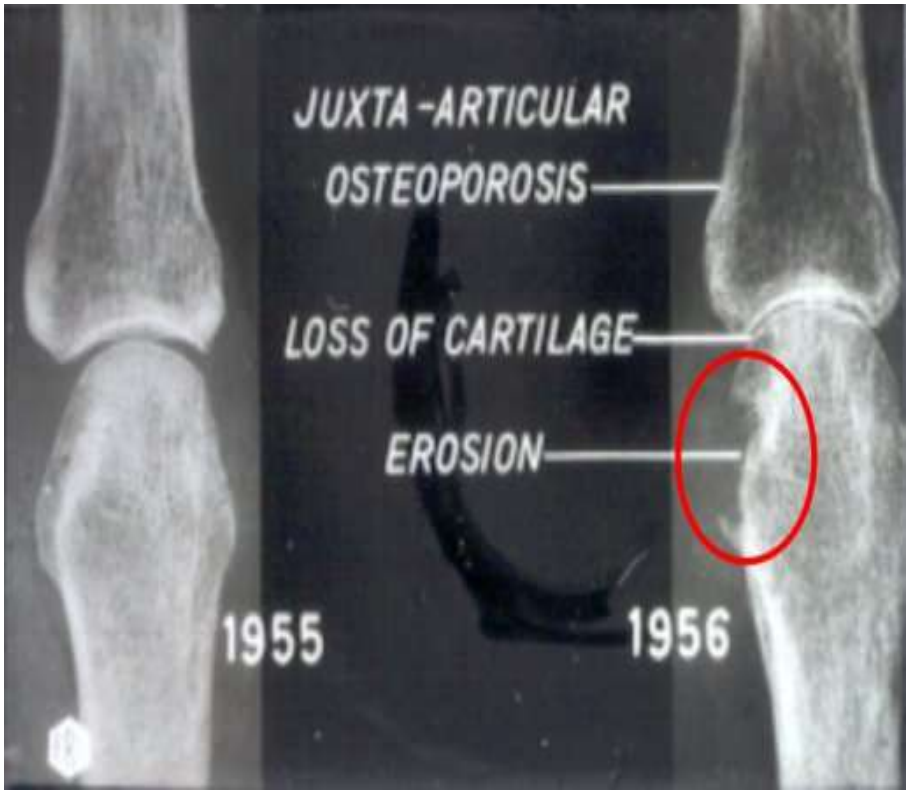
2. Resistance to apoptosis associated include abnormalities of tumor protein p53 function, which contributes to synovial lining expansion and joint destruction in RA.

3. Over expression of heat shock protein 70 and enhanced activation of heat shock factor 1 in RA synovial tissues that foster the survival of FLS

Bone erosion

- Pathological hallmark of RA and manifests as localized, periarticular and systemic bone loss.
- Induction of osteoclasts and the suppression of osteoblasts.
- “Periarticular” bone loss refers to cellular changes of the subchondral bone marrow, such as osteoclast differentiation and the formation of inflammatory infiltrates.
- Theory for Bone damage

1. Inflammatory Theory
2. Autoimmunity



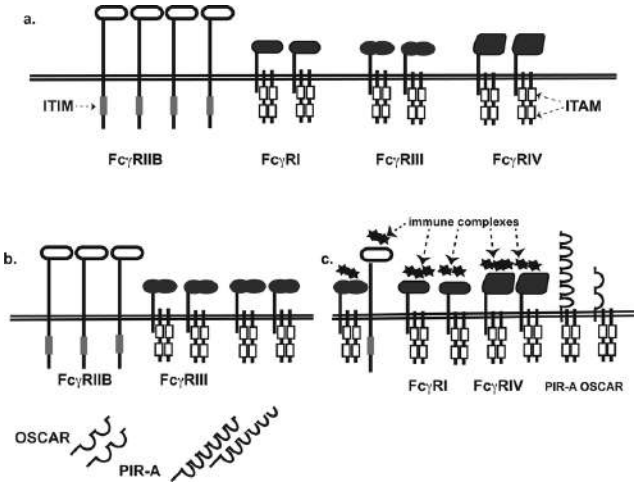
Inflammatory Theory

- Tumor necrosis factor alpha (TNF-α), IL-6, IL-1β, IL-17, and other inflammatory cytokines involved in RA could exert pro-osteoclastogenic effects and suppress bone formation in the appropriate environment via adequate signals, such as the receptor activator of nuclear factor kappa-B ligand (RANKL) and macrophage colony-stimulating factor (M-CSF).
- These promote the influx and differentiation of the monocytes into osteoclasts in the context of inflammation.

Autoimmunity

1. Formation of immune complex and Fc-receptor-mediated osteoclast differentiation.
2. Formation of anti-citrullinated vimentin antibodies against the most citrullinated protein, making osteoclasts the ideal antigenic targets for anti-citrullinated protein antibodies (ACPA).

ACPA binding to osteoclast precursors induces osteoclastogenesis, bone resorption, and bone loss.



Management

Goals of management

- Focused on relieving pain
- Preventing damage/disability
- Patient education about the disease
- Physical Therapy for stretching and range of motion exercises
- Occupational Therapy for splints and adaptive devices
- Treatment should be started early and should be individualised .
- ***EARLY AGGRESSIVE TREATEMNT***

Treatment modalities for RA

- NSAIDS
- Steroids
- DMARDs
- Immunosuppressive therapy
- Biological therapies
- Surgery

- **Non-Steroidal anti-inflammatories (NSAIDS) / Coxibs for symptom control**

1) Reduce pain and swelling by inhibiting COX
2) Do not alter course of the disease.
3) Chronic use should be minimised.
4) Most common side effect related to GI tract.

Corticosteroids in RA

- Corticosteroids , both systemic and intra-articular are important adjuncts in management of RA.
- Indications for systemic steroids are:-
  1. For treatment of rheumatoid flares.
  2. For extra-articular RA like rheumatoid vasculitis and interstitial lung disease.
  3. As ***bridge therapy*** for 6-8 weeks before the action of DMARDs begin.
  4. Maintainence dose of 10mg or less of predinisolone daily in patients with active RA.
  5. Sometimes in pregnancy when other DMARDs cannot be used.

Disease Modifying Anti-rheumatic Agents

- Immunosuppressive and immunomodulatory agents and are classified as either conventional DMARDs or biologic DMARDs.
- Commonly used conventional DMARDs include methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine.
- Biologic DMARDs were introduced in the early 1990s and are usually prescribed after the failure of conventional DMARD therapy (ongoing disease activity or clinical or radiographic disease progression).
- Some biologic agents include infliximab, adalimumab, etanercept, rituximab, abatacept, rituximab, tocilizumab, tofacitinib, among others.

DMARDs

Commonly used	Less commonly used
Methotrexate	Chloroquine
Hydroxychloroquine	Gold(parenteral &oral)
Sulphasalazine	CyclosporineA
Leflunomide	D-penicillamine/bucillamine
	Minocycline/Doxycycline Levamisole
	Azathioprine,cyclophosphamide, chlorambucil

Clinical information about DMARDs

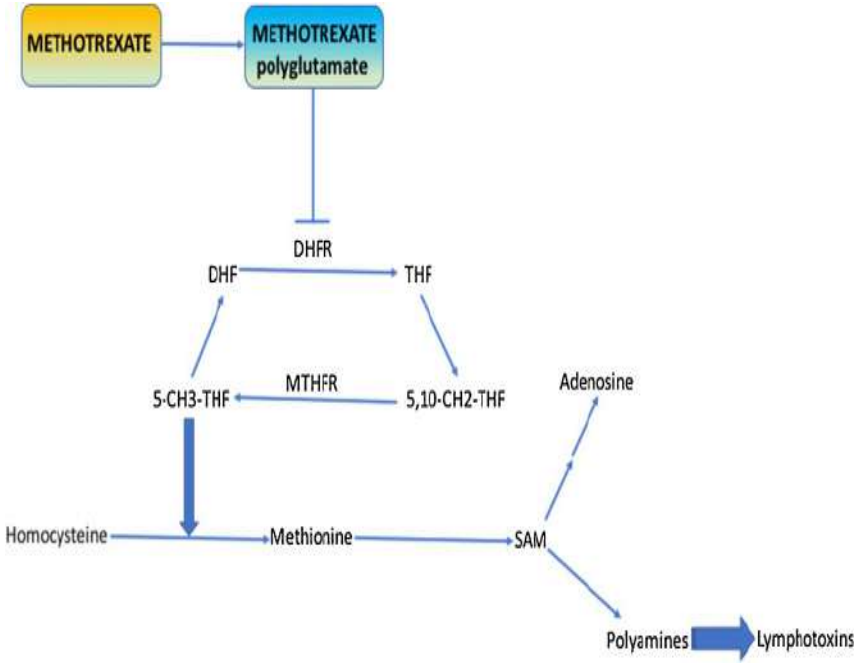
NAME	DOSE	SIDE EFFECTS	MONITORING	ONSET OF ACTION
1) Hydroxychloroquine	200mg twice daily x 3 months, then once daily	Skin pigmentation , retinopahy ,nausea, psychosis, myopathy	Fundoscopy& perimetry yearly	2-4 months
2) Methotrexate	7.5-25 mg once a week orally,s/c or i/m	GI upset, hepatotoxicity, Bone marrow suppression, pulmonary fibrosis	Blood counts,LFT 6-8 weekly,Chest x-ray annually, urea/creatinine 3 monthly; Liver biopsy	1-2 months

Clinical information about DMARDs contnd..

NAME	DOSE	SIDE EFFECTS	MONITORING	ONSET OF ACTION
3)Sulphasala-	2gm daily p.o	Rash, myelosuppression, may reduce sperm count	Blood counts ,LFT 6-8 weekly	1-2 months
4)Leflunomide	Loading 100 mg daily x 3 days, then 10-20 mg daily p.o	Nausea,diarrhoea,alopecia, hepatotoxicity	LFT 6-8 weekly	1-2 months

Methotrexate

- MTX is a modified form of folate designed to have an increased binding affinity for dihydrofolate reductase (DHFR) compared with its parent molecule.
- MTX has been proposed to participate in the process of folate antagonism, adenosine signaling, the blocking of methyl-donor production involved in reactive oxygen species, downregulation of the adhesion-molecule expression, modification of cytokine profiles, and the downregulation of eicosanoids and MMPs.



By inhibiting DHFR, methotrexate depletes levels of tetrahydrofolate and methyltetrahydrofolate (5-CH3-THF) (Fig. 3). These two compounds normally act as methyl donors to form methionine and S-adenosylmethionine (SAM). These two molecules are also methyl group donors and they lead to the formation of polyamines

Leflunomide

- Leflunomide reduces inflammation in the joints of RA patients by inhibiting dihydroorotate enzymes essential for producing DNA and RNA, particularly in activated proliferation lymphocytes.
- At higher doses, the active metabolite teriflunomide also inhibits tyrosine kinases responsible for early T-cell and B-cell signaling.
- Drug interactions -- Cholestyramine that impairs the absorption of Leflunomide, rifampin side effects caused by raising Leflunomide levels in the blood, and Leflunomide rarely increasing the anticoagulant effect of warfarin.
- Leflunomide should be avoided during pregnancy and lactation

- Most common reported side effects

❖ Diarrhea, nausea, headache, rash, itching, loss of hair and body weight, hypertension, chest pain, palpitation, infection, and liver failure.

Sulfasalazine (SSZ)

- Anti-inflammatory and antimicrobial activities.
- Its metabolites are sulfapyridine and 5-aminosalicylic acid (5-ASA).
- SSZ has the ability

❖ to increase the production of adenosine at the sites of inflammation;

❖ inhibit osteoclast formation via modulatory effects on the receptor activator of nuclear factor κβ (RANK), osteoprotegerin, and RANKL, inhibit TNF-α expression via the apoptosis of macrophages, and

❖ suppress B-cell function.

- Sulfapyridine may reduce IL-8 and monocyte chemotactic protein 1 (MCP-1) secretions in inflammatory cytokines.
- The common adverse effects of M: SSZ include gastrointestinal and central nervous system toxicity, rash, liver function abnormalities, leukopenia and agranulocytosis, megaloblastic anemia, oligospermia, and infertility.

ADVERSE EFFECT

- Methotrexate, leflunomide, and sulfasalazine are similar in their adverse effect profile.
- Gastrointestinal distress (nausea, abdominal pain, diarrhea), rash/allergic reaction, bone marrow suppression, hepatotoxicity, are common adverse effects of all these agents.
- Both methotrexate and leflunomide can cause alopecia.
- Methotrexate : interstitial lung disease, folic acid deficiency, and liver cirrhosis.
- Leflunomide : hypertension, peripheral neuropathy, and weight loss.
- Sulfasalazine has a very high risk of gastrointestinal distress. It can rarely cause DRESS syndrome as well.

Hydroxychloroquine

- Interfere with the interaction between T helper cells and antigen-presenting macrophages that cause joint inflammation and decrease the production of pro-inflammatory cytokines, thus reducing the overall inflammatory response.
- Hydroxychloroquine impaired phago/lysosomal function, it also appears to work in a lysosome-independent manner by impacting on intracellular TLRs, particularly TLR9, by inhibiting the production of TNF, and by interfering with the processing of the conversion of the membrane-bound pro-TNF into soluble mature protein.
- Hydroxychloroquine has a gradual onset action of 2–6 months, demonstrating improvement of long-term functional outcome and retardation of radiographic damage.
- The common adverse effects are predominantly gastrointestinal, dermatological, and ophthalmologic.

- Hydroxychloroquine..Compared to other conventional DMARDs, does not increase the risk of severe infections, nor does it cause hepatotoxicity or renal dysfunction.
- Common adverse effects of hydroxychloroquine include rash, diarrhea.
- A rare but significant adverse effect of hydroxychloroquine is retinopathy/maculopathy, which is seen with a higher cumulative dose.
- Risk factors for hydroxychloroquine maculopathy include more than 5 mg/kg/day dose, more than 5 years of therapy, advancing age, and chronic kidney disease.

Immunosuppresive therapy

Agent	Usual dose/route	Side effects
Azathioprine	50-150 mg orally	GI side effects , myelosuppression, infection,
Cyclosporin A	3-5 mg/kg/day	Nephrotoxic , hypertension , hyperkalemia
Cyclophosphamide	50 -150 mg orally	Myelosuppression , gonadal toxicity ,hemorrhagic cystitis , bladder cancer

TNF-α inhibitor (TNFi)

TNF-α triggers inflammatory responses and is produced by activated monocytes, macrophages, and T lymphocytes.

TNF-α acts through TNF receptors 1 and 2, interaction of TNFα and its receptors, key signaling pathways can be activated, such as the NF-κB pathway, RANKL signaling, the extracellular signal-regulated kinase (ERK) signaling pathway, the tumor progression locus 2 (TPL2) pathway, and proapoptotic signaling.

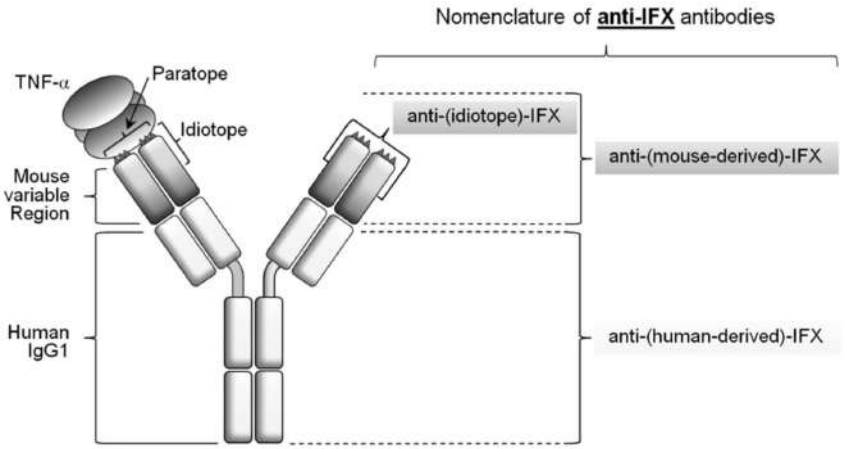
TNF has been involved in the process of endothelial cell activation, the induction of metalloproteinases and adhesion molecules, angiogenesis, and the regulation of fibroblast/keratinocyte/enterocyte chondrocyte/osteoclast activation, as well as other inflammatory cytokines.

Agent	Usual dose/route	Side effects	Contraindications
Infliximab (Anti-TNF)	3 mg/kg i.v infusion at wks 0,2 and 6 followed by maintainence dosing every 8 wks Has to be combined with MTX.	Infusion reactions, increased risk of infection, reactivation of TB ,etc	Active infections, uncontrolled DM, surgery(with hold for 2 wks post op)
Etanercept (Anti-TNF)	25 mg s/c twice a wk May be given with MTX or as monotherapy.	Injection site reaction,URTI , reactivation of TB,development of ANA,exacerbation of demyelenating disease.	Active infections, uncontrolled DM, surgery(with hold for 2 wks post op)
Adalimumab (Anti-TNF)	40 mg s/c every 2 wks(fornightly) May be given with MTX or as	Same as that of infliximab	Active infections

Infliximab (IFX)

- Infliximab (IFX) was the first TNFi for RA treatment and consists of a recombinant chimeric monoclonal antibody composed of a human antibody backbone with a mouse idiotype.

- It can neutralize the biological activity of TNF-α by binding all forms of TNF-α.



Adalimumab (Ada)

- Adalimumab (Ada) is a fully humanized anti-TNF-α monoclonal antibody given by subcutaneous route fortnightly and has a less pronounced toxicity profile.

Etanercept

- Etanercept is a recombinant protein composed of an immunoglobulin backbone and two naturally occurring soluble human 75-kDa TNF receptors.
- It is given by subcutaneous route twice weekly with toxicity profiles similar to IFX and Ada.

Small-molecule DMARDs--- JAK pathway

- Tofacitinib is the first of a new class of oral drugs to have synthetic small molecules that interfere with specific signal-transduction pathway and is the third class of DMARD (tsDMARDs) in RA treatment.

- Preferentially inhibits JAK-3 and -1 over JAK-2.

- With an oral bioavailability of 74% and mean elimination half-life of 3 h, tofacitinib is metabolized via cytochrome P450 3A4 (CYP3A4) with 30% renally excreted; 5 mg bd Tofacitinib has recently been approved by the FDA for moderate to severe RA refractory to DMARDs

Baricitinib

- Orally administered molecular that inhibits JAK-1 and -2.
- It has moderate activity on tyrosine kinase 2 (TYK2)and negligible activity on JAK-3 in both enzymatic and cellular assays.
- Peficitinib showed a 14 times higher selectivity for JAK-1/-3 over JAK-2.
- ABT-494 is also a JAK-1 selective Jakinib.

JAK pathway

Name	Mechanism of action	Potential mechanisms	Side Effect
1. Tofacitinib	JAK1 and JAK3 inhibitor	T-cell activation, pro-inflammatory cytokine production, synovial inflammation, and structural joint damage.	Zoster infection (advice is to vaccinate beforehand) and other potential side-effects should be monitored carefully through further study.
2. Baricitinib	JAK1 and JAK2 inhibitor		
3. Filgotinib	JAK1 inhibitor		

IL-1 inhibition

- Anakinra (rHuIL-1ra) is a non-glycosylated recombinant form of the IL-1 receptor antagonist used as a once daily injectable.
- It is different from the native human protein by having an additional N-terminal methionine.
- It decreases the activity of IL-1α and IL-1β by binding to the IL-1 receptor.

Secukinumab

- IL-17 inhibitor (Secukinumab) was finished in a phase III study displaying improvement in patients with active RA who had an inadequate response to TNF inhibitors

Golimumab

- Golimumab is a human IgG1 kappa monoclonal antibody that binds to both the soluble and transmembrane bioactive forms of human TNF-α.
- It is administered once monthly by subcutaneous injection.

Certolizumab pegol

- Certolizumab pegol is a human anti-TNF-α antibody Fab fragment that is chemically linked to polyethylene glycol and neutralizes membrane-associated and soluble TNF-α.
- It is administered every 2 weeks by subcutaneous injection.

Rituximab

- Rituximab is a genetically engineered chimeric monoclonal antibody that targets CD20-positive B lymphocytes from early pre-B-cells to later in the differentiation process, but it is absent in terminally differentiated plasma cells.
- The binding to CD20 enables rituximab to deplete subpopulations of B lymphocytes by way of cell-mediation, complement-dependent cytotoxicity, and the promotion of apoptosis and growth arrest.

Belimumab

- Belimumab is a monoclonal anti-B lymphocyte stimulator (BLyS) antibody.
- It binds to soluble human BLyS with high affinity and inhibits its biological activity.
- The BLyS mechanism of action of is importance in the survival of B cells, and its inhibition can lead to the apoptosis of autoimmune B-cell clones.

Abatacept

- Abatacept is a T-cell co-stimulation modulator and a fully human soluble fusion protein that consists of the extracellular domain of human CTLA-4, which is linked to the modified Fc part of human IgG1.
- T-cells infiltrate into the synovial joint and increase the level of pro-inflammatory cytokines such as interferon-γ and IL-17, causing synovial cartilage and bone destruction.
- Upon antigen recognition, T-cells require a costimulatory signal for full activation.

Tocilizumab (TCZ)

- Tocilizumab (TCZ) is a humanized monoclonal antibody that targets the IL-6 receptor, which is found on cell surfaces and in circulation.
- IL-6 is produced by various cell types, including T cells, B cells, monocytes, fibroblasts, and endothelial and synovial cells.
- It has two receptors: mIL-6R (CD 126) and sIL-6R.
- *In the pathology of RA, IL-6 can stimulate pannus formation through increased vascular endothelial growth factor expression and increase bone resorption as a result of osteoclastogenesis, as well as oxidative stress in leukocytes*

Agent	Usual dose/route	Side effects	Contraindications
(Anti-IL-1) Anakinra	100 mg s/c once daily May be given with MTX or as monotherapy.	Injection site pain,infections, neutropenia	Active infections
Abatacept (CTLA-4-IgG1 Fusion protien) Co-stimulation inhibitor	10 mg/ kg body wt. At 0, 2 , 4 wks & then 4wkly	Infections, infusion reactions	Active infection TB Concomittant with other anti-TNF-α
Rituximab (Anti CD20)	1000 mg iv at 0, 2, 24 wks	Infusion reactions Infections	Same as above
Tocilizumab (Anti IL-6)	4-8 mg/kg 8 mg/kg iv monthly	Infections, infusion reactions,dyslipidemia	Active infections

Growth and differentiation factors

Name	Mechanism of action	Potential mechanisms	Side Effect
Denosumab	RANKL inhibitor	Maturation and activation of osteoclast.	Low Ca2+ and phosphate in the blood, muscle cramps, cellulitis, and numbness.
Mavrilimumab	GM-CSF inhibitor	Activation, differentiation, and survival of macrophages, dendritic cells, and neutrophils; T helper 1/17 cell; modulation of pain pathways.	Safety file needs further research.

Osteoclast differentiation factor

- Denosumab (DMab) is a human monoclonal IgG2 antibody that inhibits bone resorption by binding and inhibiting the receptor activator of the NF-kB ligand (RANKL), an essential cytokine for osteoclastogenesis and bone resorption. Briefly, RANKL is an essential survival factor for DCs.

I. RANKL-expressing Th17 cells mediate bone resorption.

II. RANKL secreted by memory B cells promotes bone erosion in RA.

III. RANKL was known to induce immune tolerance by promoting the differentiation of Treg cells.

The side effects include low Ca2+ and phosphate levels in the blood, muscle cramps, cellulitis, and numbness.

Monitoring

1. Prior to starting a DMARD, patients shall be screened for hepatitis B and C. Additionally, screening for tuberculosis is strongly recommended before initiating any biologic DMARD.
2. In women of childbearing age, a pregnancy test shall be done before initiating these agents.
3. Myelosuppression and hepatotoxicity are more common early in therapy
4. Complete blood count and liver function test shall be performed monthly for at least 3 months initially, and every 2 to 3 months thereafter in patients initiated on agents including methotrexate, leflunomide, sulfasalazine, tocilizumab, tofacitinib, and sarilumab.
5. Lipid panel shall be monitored at baseline and then every 3 months for at least 6 months and then every 6 months thereafter in patients initiated on tocilizumab, tofacitinib, and sarilumab.

- CBC shall be monitored every 6 months in patients on any of the biologic DMARDs.
- Since many of these agents require dose adjustment in renal insufficiency, close monitoring of renal function every 3 to 6 months is also recommended in patients on DMARDs.
- Comprehensive ophthalmology exams including visual field testing and ocular coherence tomography are necessary at baseline, at 5 years, and then annually in patients on hydroxychloroquine.

When to start DMARDs?

- DMARDs are indicated in all patients with RA who continue to have active disease even after 3 months of NSAIDS use.
- The period of 3 months is arbitary & has been chosen since a small percentage of patients may go in spontaneous remission.
- The vast majority , however , need DMARDs and many rheumatologists start DMARDs from ***Day 1.***

How to select DMARDs?

- There are no strict guidelines about which DMARDs to start first in an individual.
- Methotrexate has rapid onset of action than other DMARD.
- Taking in account patient tolerance, cost considerations and ease of once weekly oral administration ***METHOTREXATE*** **is the** DMARD of choice, most widely prescribed in the world.

Should DMARDs be used singly or in combination?

- Since single DMARD therapy (in conjunction with NSAIDS) is often only modestly effective , combination therapy has an inherent appeal.

- DMARD combination is specially effective if they include ***methotrexate*** as an anchor drug.

- **Combination of methotrexate with leflunamide** are synergestic since there mode of action is different.

Limitations of conventional DMARDs

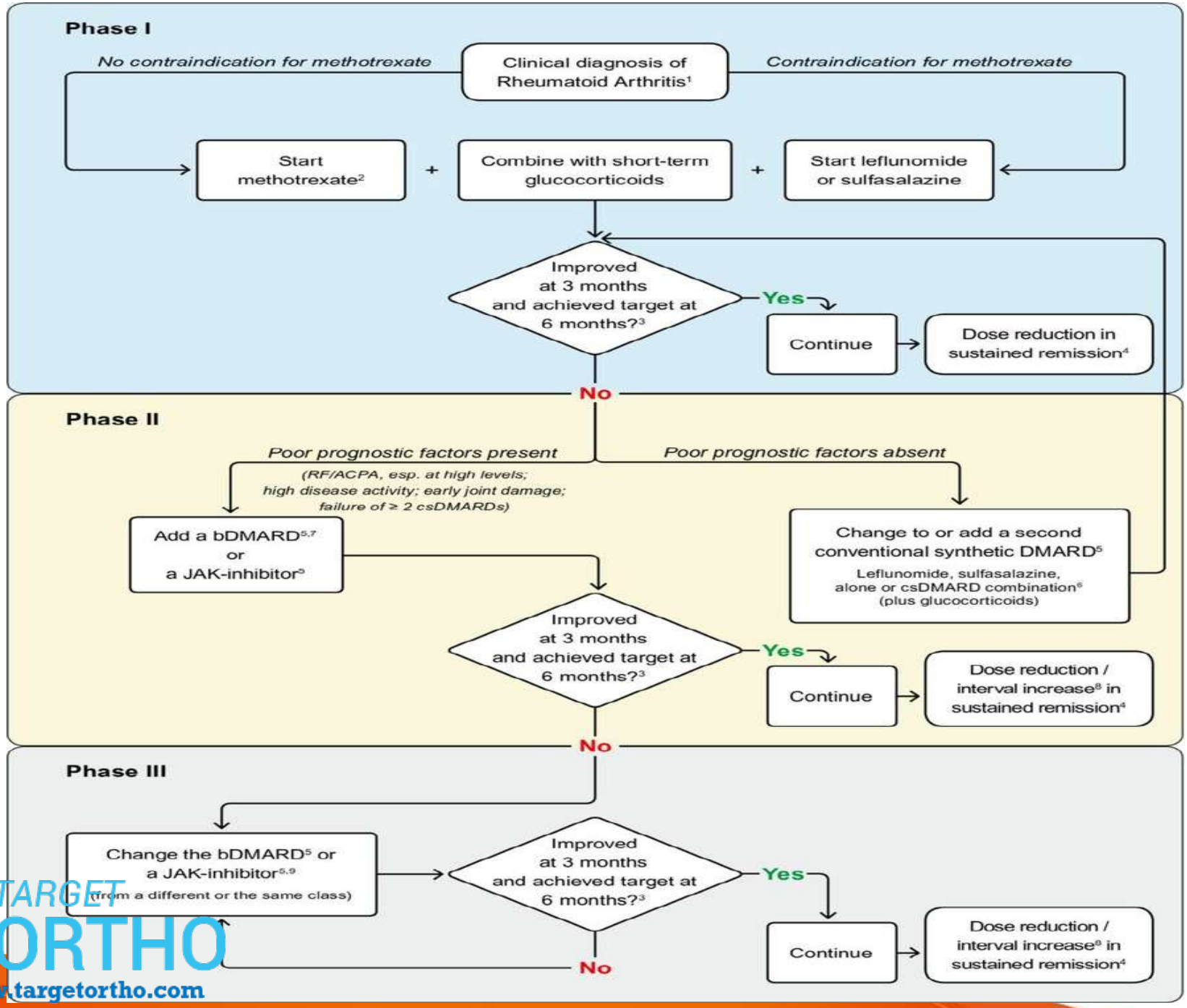
1) The onset of action takes several months.
2) The remission induced in many cases is partial.
3) There may be substantial toxicity which requires careful monitoring.
4) DMARDs have a tendency to lose effectiveness with time-(slip out).

- These drawbacks have made researchers look for alternative treatment strategies for RA- **The Biologic Response Modifiers.**

BIOLOGICS IN RA

- Cytokines such as TNF-α ,IL-1,IL-10 etc. are key mediators of immune function in RA and have been major targets of therapeutic manipulations in RA.
- Of the various cytokines,TNF-α has attaracted maximum attention.
- Various biologicals approved in RA are:-

1) Anti TNF agents : Infliximab Etanercept Adalimumab
2) IL-1 receptor antagonist : Anakinra
3) IL-6 receptor antagonist : Tocilizumab
4) Anti CD20 antibody : Rituximab
5) T cell costimulatory inhibitor : Abatacept



How to monitor Tt in RA?

- Disease activity is assesed by several parameters…
  - Duration of morning stiffness
  - Tender joints count
  - Swollen joints count
  - Observer global assessment
  - Patient global assessment
  - Visual analogue scale for pain
  - Health assessment questionnaire
  - ESR
  - NSAID pill count etc…

- Patient on MTX, SSZ or leflunamide show clinical improvement in 6-8 wks.

- Patient should be observed for 6 months before declaring a DMARD ineffective.

How long should Tt. be continued?

- Once remission is achieved , maintenance dose for long period is recommended.
- Relapse occurs in 3-5 months (1-2 months in case of MTX) if drug is discontinued in most instances.
- DMARDs are discontinued by patients because of **toxicity** or **secondary failure**(common after 1-2 yrs) and such patients might have to shift over different DMARDs over 5-10 yrs.
- Disease flare may require escalation of DMARD dose with short course of steroids.

Surgical Approaches

- Synovectomy is ordinarily not recommended for patients with rheumatoid arthritis, primarily because relief is only transient.
- An exception is synovectomy of the wrist, which is recommended if intense synovitis is persistent despite medical treatment over 6 to 12 months.
- Persistent synovitis involving the dorsal compartments of the wrist can lead to extensor tendon sheath rupture resulting in severe disability of hand function.
- Total joint arthroplasties , particularly of the knee, hip, wrist, and elbow, are highly successful.
- Other operations include release of nerve entrapments (e.g., carpal tunnel syndrome), arthroscopic procedures, and, occasionally, removal of a symptomatic rheumatoid nodule.

Future drug and target

- Toll like receptors
- Bruton's tyrosine kinase
- Phosphoinositide-3-kinase pathway
- Transforming growth factor-beta
- Neuropathways
- Dendritic cell

Thank you.

FOR ANY QUERIES-
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