PC
Pharmacology Concepts
By Rajesh Choudhary

Anti Gout & RA Drugs

Pharmacology 2 | U2

GOUT

↳ Very painful form of arthritis characterized by formation of "Uric Acid Crystals" & sever inflammation.

↳ Purine metabolic disorder, Leads to "Hyperuricamia" (> 6 mg/dL). Hyperuricamia occurs due to ↑ production & ↓ Excretion

P° Hyperuricemia Vs 2° Hyperuricamia

Uric Acid Metabolism –

RNA/DNA → Purines → (PRPP) Hypoxanthines → (Xanthine Oxidase) Xanthines → (Xanthine Oxidase) URIC ACID

Allopurinol (–) on Xanthine Oxidase

URIC ACID → Hyperuricamia → Gout

URIC ACID → Deposit° of urate crystal → Nephrolithiasis

PATHOPHYIOLOGY :–

↑↑ Blood Uric Acid

↓ sodium

Sodium Crystals (Tophi)

(Deposition in soft tissue & Joints)

↓ (–) NSAIDs

INFLAMMATORY

Phagocyte → release H^+

$H^+ + A^-$ (urate) → HA (unionized Crystal) ↑↑

Colchicine

Inflammatory → Free Radicals → Tissue Damage

Pain/U.Crystal → lactic ā → Release Proteolytic Enz

Release of lysozyme

↓

Joint Destruction

Risk Factor: -- Red meat, Beans, Alcohol, Fish

Etiology –

① Enzyme Defect – ↑ product° of UA

② Diet

③ Renal Failure – ↓ Excret° of UA

④ Cancer Treatment – Chemo / Radio

⑤ Diabetes Malitus / Obesity

Types –

① Acute
2. Chronic

① Primary
② Secondary

GOUT

1. Acute Gout

- Sudden Painful Arthritic Attack
- Occuring at night or early morning
- Generally involve one or few joints
- Common Site - Metatarsophalangeal joints
- Other - Ankle, heel, knee, wrist, elbow

Drugs -

- NSAIDs
- Corticosteroids
- colchicine

2. Chronic Gout

- ↑ Frequently attack & chronic pain
- May develope large stones/crystal
- Lead to kidney stones
- Articular cartilage may be destroyed result in joint deformities

Drugs -

Uric Acid Synthesis Inhibitor (Urostatics) :- Allopurinol, Febuxostate

↑ UA Excretion (Uricosurics) – Probencid, Sulphinpyrazole

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COLCHICINE

"Colchicum autumnale" (Since 1763, used in Gout)
Pure alkaloid "colchicine" isolated in 1820
Neither Analgesic nor Anti-inflammatory
Specifically Supress the Gout inflammation.
It does not inhibit the Synthesis or promote the excretion of uric acid.

MOA = ↓ Migration (Chemotaxis) of Granulocyte

Acute Attack ⟶ ↑ Ureate crystal at Joints

↓

Acute Inflammatory Response

↓

Phagocytes the crystal by granulocyte and release glycoprotein

↓

↓ pH → ↑ Ureate crystals
→ ↑ Lactic acid – inflamatn
→ ↑ lysosomal Enz → Joint destruction

Cholchicine – tubulin → ↓ Polymerizatn of Microtubules

↓

↓ chemotactic factor & chemotaxis of Granulocytes ← ↓ Phagocytic Action

Others ⓐ Antimitotic – Arrest metaphase
ⓑ ↑ Gut motility (Neural mechanism)

P'kinetic – oral active, Metabolized in liver, Excrete through bile, undergoes enterohepatic circulatn. ultimate desposal through urine

ADR :-

High & dose related Nausea, Vomiting, Diarrhoea, & abdominal Cramps
In Overdose – Kidney damage, CNS depression GI bleeding, Death due to Respiratory failure & muscular paralysis

Use:-

Acute Attack of Gout (0.5mg tab for 1-3 h) 3-4 doses in a day
Max 6 mg over 3-4 days

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RHEUMATOID ARTHRITIS

↳ Most common cause of "chronic inflammatory Joint Disease"

↳ Also a "Systemic Autoimmune disease"

↳ charecterized by Joint inflammation, Synovial Proliferation, & distruction of articular cartilage

↳ Feature – ① Morning Stiffness ② ↑ ESR ③ A Symmetrical polyarthritis & tenosynovitis ④ Autoantibodies that target Igs in Serum

9t affect 1-3 /. World wide, 30-50 Y Age

Woman 4 : 1 Man

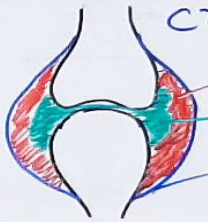
↳ Etiology :- ① Genetic ② Immunological Reaction ③ chronic Inflammation ④ ↑ Serum & Synovium Rheumatoid factors

↳ PATHOPHYSIOLOGY :-

Immune Complexes – IgM components → chemotaxis (Neutrophil) ← IL-1, TNF-α

Lysozymes → Damage cartilage & Bone

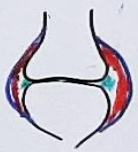
PGs → Inflammatory Response



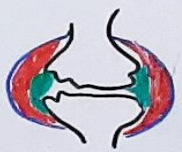
cross sechonal Joint
Inflammed Synovial membrane
Excess Joint fluid
Joint Capsule

Clinical Pathology :-

stage 1 → # Immune Pathology begin, ↑ ESR, ↑ C-reactive protein, & ↑ Rheumatoid factors

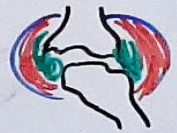


Stage 2 (Synovial) # Vascular Hyperplesia # Synovial Proliferation # Infilteration # Thickening of Capsule



Stage 3 (Destruction)

Destruct^n of Joint cartilage & tendon
Swelling & Inflammat^n Reaction
Bone is also ended by granulat^n tissue invasion and Osteoclastic Resorption



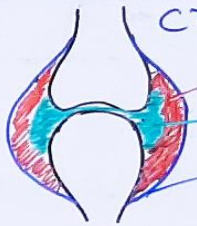
Stage 4 (Deformity)

Destruction alongwith Deformities
Inable of functioning
Synovitis
Secondary Complication

RHEUMATOID ARTHRITIS

Clinical Feature –

- Late Stage →
  1. Pain, deformity, instability
  2. Joint – restrictive to movements
- Thumb → Z- Deformity
- Fingres – Swan neck deformity
- Wrist – Radial & Volar desplacement
- Elbo – Limited Extension
- Knees – Swollen
- Toes – Clawed



cross sechonal Joint
Inflammed Synovial membrane
Excess Joint Fluid
Joint Capsule

DRUGS

I. Disease Modifying Anti-Rheumatoid drugs (DMARDs)

A. Non Biological –

↳ Immunosupressants – Methotrexate, Azathioprine, Cyclosporine

↳ Other Immunomodulator – Sulfasalazine Hydroxychloroquine, etc

B. Biological –

↳ TNF α Inhibitor – Etanercept, Infliximab

↳ other – Anakinra, Rituximab

ANTI-RHEUMATOID DRUGS

The drugs which can supress the rheumatoid process.

I) Disease Modifying Antirheumatoid Drugs (DMARDs)

→ A) Non-Biological

* Immuno supressant :→ Methotrexate, Azathioprine, Cyclosporine
* Immuno-modulators = Sulfasalazine, Hydroxychloroquine, Leflunomide, Tofaticinib

Biological Role :- (—)

"Supress the Immune/Inflammatory Response"

↳ ↓ Cytokines (IL & TNFα) Production
↳ ↓ Cell proliferation
↳ ↓ Cell mediated immune response
↳ ↓↓ Progression of RA

MTX = 1st choice DMARDs, use single or combinations,
= Symptomatic relief after 3-6 weeks
= DHFR Inhibitor (Anticancer Drugs)

AZT = Purine syn. Inhibitor (Anticancer Drugs)
= Selectively ↓ T-cell mediated immunity
= used along with Corticosteroids

Sulfasalazine - Anti ulcerative colitis drug
→ ↓ Inflammatn & oxidative stress
→ 2nd line of drug used along with MTX

Hydroxychloroquine → Antimalarial drug
↳ ↓ monocyte IL, B-Lymphocyte, Antigenic process and oxidative stress

Leflunomide - Inhibits proliferation of stimulated lymphocyte in RA patient, symptomatic relief (4 weeks)
MOA - Inhibits dihydro-orotate dehydrogenase & pyrimidine synthesis on B-Cell
↳ loading dose 100 mg (3 days) → 20 mg OD
↳ ADR - diarrhoea, headach, nause, hair loss, Cytopenia, leukopenia, ↑ chance of chest infection, hepatotoxic (Not used in children, pregnant, Lactating mother)
↳ Use alternative to Mtx or in combination with Sulfasalazine

Tofaticinib - New Synthetic drug for sever RA, those not respond to MTx
↳ Inhibit JAK-3 & JAK-1 → JAK-STAT — DNA Transcription
↳ Used alone or along with MTX, but not with AZT, Cyclosporine, and other Biological DMARDs
↳ ADR - headach, insomnia, diarrhoea, hypertension, anemia, respiratory infect^{n}, Liver damage

ANTI-RHEUMATOID DRUGS

The drugs which can supress the rheumatoid process.

2) Biological Agents

TNF-α Inhibitors → Etanercept, Infliximab, Adalimunab

Others - Anakinra, Abatacept, Rituximab

* rProtein/Monoclonal antibodies → ⇓ Cytokines (IL-1 & TNFα)

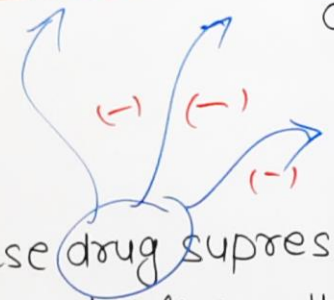
↳ Used only as reserve drugs for several inf. diseases

TNF-α Inhibitors

↳ In RA, TNFα → (+) $TNFR_1$ & $TNFR_2$ (on the surface of T cells & Macrophages)

↓

Inflammatory & Immune Responce



↳ These drug supress the action of Tcells & Macrophage by neutralizing the TNF-α and ⇓ Rheumatoid progress

↳ Quick response than non biological DMARDs

↳ They are effective in monotherapy & can be added with Mtx

↳ Enhance the risk of Granulomatous infection like Tuberculosis, Pneumocystis pneumonia.

Etanercept = r. fusion protein of TNFR with Fc protein of human IgG_1 (50 mg/weak, sc) → TNFR

Infiximab = chimeral monoclonal antibody which neutralize TNFα (3-5 mg/kg, IV, every 4-8 weaks)

Adalimunab = r. human monoclonal antibody (40 mg/2weeks, sc)

Anakinra - r. human IL-1 R antagonist (low eficacy)

Abatacept - r. fusion protein (Fc protein of IgG_1 & Tcell inhibitory receptor, CTLA4)

↳ Approved for moderate to sever RA not responding to MTx

CORTICOSTEROIDS

↳ Potent Antiinflammatory & Immunosupressants

↳ It can be used any stage of RA along with DMARDs

↳ Symptomatic relief, but not arrest the rheumatoid process

↳ Long term shows dengerous side effects, so →

↳ low dose (5-7.5 mg prednisolone)

↳ high dose if required, short periode

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