Rheumatoid arthritis

- Chronic autoimmune disease
  - inflammation of the joints and other areas of the body.
- no known cure
- periods of disease flares and remissions.
- Chronic inflammation leads to destruction of the cartilage, bone and ligaments causing deformity of the joints.
- Can cause permanent joint destruction and deformity.
- Early treatment of rheumatoid arthritis results in better outcomes.
Rheumatoid Arthritis (RA)
Pathophysiology

- **Cause** – unknown
- **Autoimmune** – most widely accepted theory
  - Antigen/abnormal Immunoglobulin G (IgG)
  - Presence of autoantibodies – **rheumatoid factor**
  - IgG + rheumatoid factor form deposits on synovial membranes & articular cartilage
    - Inflammation results – pannus (granulation tissue at the joint margins) – articular cartilage destruction---**cytokines IL-1 & TNF α** imp role
- **Genetic** – predisposition/familial occurrence of “human leukocyte antigen (HLA) in white RA patients
Rheumatoid arthritis (late stage)

Boutonniere deformity of thumb

Ulnar deviation of metacarpophalangeal joints

Swan-neck deformity of fingers
**Fig 26.3**

Pathogenesis of Rheumatoid Joint Damage and Sites of Action of Antirheumatoid Drugs.
DMARDS: Disease Modifying anti-rheumatic drugs

- **IMMUNOMODULATORS**
- **METHOTREXATE:**
  - DMARD of 1st choice for RA used in 50-70% pts
  - MOA: used in low doses – inhibition of AICAR & thymidylate synthetase.
  - Also has secondary effects on PMN chemotaxis.
  - Some effect on DHFRase - effects lympho & macro function.
  - Direct inhibitory effect on prolif + stimulates apoptosis in immune-inflamm cells.
  - Inhibits proinflamm cytokines
Methotrexate...

- **PK**: 70% absb PO, metab to less active metabolite, both are polyglutamated within cells –stay for prolonged pd. Plasma T1/2 6-9hrs. HCQ increases it’s conc. Excreted prim in urine, also in bile –upto 30%

- **Use**: RA: 15-25 mg weekly. Decreases rate of appearance of new erosions. Also in JCA, AS, Wegener’s, SLE.
Methotrexate...

- **A/E**: N, mucosal ulcers - moderate common.
- Dose related hepatotoxicity - raised liver enz common. Lung damage - hypersensitivity rxn & pseudo lymphomatous rxn.
- Leucovorin 24hrs after weekly dose / daily FA useful
- **CI** in pregnancy
Leflunomide

- MOA: acts thru active metabolite—arrest of stimulated cells in G1----inhibits T−cell prolif & autoantibody prod by B-cells
- PK: t1/2 19days, enterohepatic cir,
- Use: RA: 100mg daily 3days---then 20 mg OD. Effective as metho, c/b combined also.
- A/E. diarrhoea-25%, H, N, rashes, mild alopecia incr hepatic enz. Cholestyramine can increase excretion.
- CI in pregnancy
Mycophenolate mofetil

• MOA: Converted to active metab mycophenolic acid--inhibits T-cell prolif. Also interferes with leuko adhesion to endoth cells.
• PK : absb PO, active metab. -enterohepatic cir—renal elim
• Use : RA : 2g/day reserved for severe RA , SLE induced renal ds
• A/E: BMD, leuko, thrombo, alopecia, hepatotoxicity, GIT tox,
• Others : Cyclosporine, Azathioprin
**BIOLOGICAL DMARDS : TNF α BLOCKING AGENTS**

- **RITUXIMAB**
- **MOA**: Chimeric mab - targets CD20B lympho --- depletion of B lympho ----↓ inflamm.
- **Use**: In RA refractory to anti TNF agents. Combined with Metho.
- **PK**: IV inf 1000mg separated by 2wks, m/b rpted q6-9mths
- **A/E**: rashes -30 % pt with 1st inf, CVS – rare
BIOLOGICAL DMARDS ...

• **Infliximab**: 

• **MOA**: Chimeric -25% mouse, 75% human IgG1 monoclonal Ab binds to soluble & memb bound **TNF α**. It inhibits T cells & macrophage fnc---prevents rel of other pro-inflam cytokines( IL6,8, collagenases & metalloproteinases)

• **PK**: IV inf- 3-5mg/kg q 8wks. T1/2 9-12days
**Infliximab....**

- **Use**: RA, AS, psoriatic arthritis, Crohns. Also being used for UC, JCA, Wegener's, sarcoidosis. In RA inflixi +metho decreases rate of form of erosions more than metho alone over 12-24 mths

- **A/E**: bact inf incid, latent TB activ., rare-leukopenia, hepatitis, vasculitis, inf site rxn. Cl in Multiple Sclerosis
Human (IgG1) Mouse binding site for TNFα

Adalimumab

All human (IgG1)

Etanercept

Human Fe (IgG1) p75 anti-TNFα receptor
BIOLOGICAL DMARDS : TNF α BLOCKING DRUGS

• **Adalimumab**

• **MOA:** fully human IgG1 anti-TNF monoclonal AB. Complexes with soluble **TNF α** & prevents interaction with p55 & p75 cell surface R---downregulation of macrophage & T-cell function

• **PK :** SC , T1/2 -10-20 days.

• **Use :** RA- 40mg q 14days –decreases rate of form of new erosions, used alone & in combi with metho . Also in AS, PA, JCA, CD.

• **A/E:** increased risk of bact inf, TB, ---. Rare-leukopenia, vasculitis
Etanercept:

**MOA:** Rt fusion prot (not Mab)—2 soluble TNF p75 R moieties linked to Fc of human IgG1—binds to TNF α mol

- **PK:** SC -25 mg twice weekly / 50 mg wkly
- **Use:** RA, Juvenile chr arth, psoriasis, Ankylosing sp. Decreases rate of form of new erosions. Used with Methotrexate inRA
- **A/E:** increased incid of bact inf, latent TB flare, oppurtunistic inf, inj site rxn
BIOLOGICICAL DMARDS.....

- **Abatacept**
  
  **MOA**: costimulation modulator – inhibits activ of T cells.

- **PK**: IV inf. In 3 initial doses, day 0, wk2, & wk4; then -monthly inf. (500-1000mg)

- **Use**: As monotherapy or along with other DMARDs in mod-sever RA. Slows progression

- **A/E**: increased risk of inf. Esp URTI. NOT combi with TNF antag. Inf related rxn
Glucocorticoids

• Provide dramatic symt relief & can slow app of new bone erosions but cause severe ADR. Used esp in cond. like pericarditis or eye involv & during exacerbations.
• Use : prednisolone <7.5 mg/d.
• Intra-articular inj of triamcinolone, hydrocortisone useful when ½ larger jnts involved
• A/E :
Gold compds : chrysotherapy

• Sodium aurothiomalate- IM, auranofin –oral.
• MOA: alters morphology & functional capabilities of macrophages. CMI suppressed. It prevents joint destruction. Aurothiamalate ↓lysosomal. Enzyme activity, ↓histamine rel form mast cells & supp. act of PMN leukos. Auronafin also inhibits rel of PGE2, LTB4, IL-1 & TNF
• PK: Accumulate in synovial fluid, liver, kidney, spleen, LN & BM. T1./2- 7days—increases with trt. So IM gold given 50 mg dose first at weekly then at monthly interval. Oral gold 6mg /d-less efficacious.
• A/E: dermatitis, hepatitis, stomatitis, ED, albuminuria, periph Neuro, pulm fibrosis, thrombo-, neutropenia. Less severe with oral
Other DMARDs

- Chloroquine and Hydroxy chloroquine
- Penicillamine: not used; toxicity
- Sulfasalazine: primarily in ulcerative colitis; sulfapyridine moiety useful not 5-ASA
- A/e: GI, H rashes, reversible decrease in sperm counts
Initial presentation with inflammatory polyarthritis

- Intra-articular or intra-muscular depot corticosteroid
- Analgia
- Proton-pump inhibitor if NSAID prescribed

Diagnosis of rheumatoid arthritis

- Introduce DMARD/comcombination of DMARDs
- Arrange monitoring of DMARDs
- Analgesia minimising use of NSAIDs

Chronic management

- Adjust DMARDs to minimise disease activity
- Change DMARDs in response to inefficacy or diverse effects
- Analgesia minimising use of NSAIODs
- Intra-articular/parenteral corticosteroids for flares
- Cardiovascular risk reduction
- Osteoprotection
- Gastroprotection
GOUT

• Inflammatory arthritis mediated by the crystallization of uric acid (MSU) within joints- tophi
• Associated with hyperuricemia
• Associations: DM, HTN, metabolic syndrome, obesity, CVD, renal stones, CPPD
• Risk Factors: genetics, age, CRF, serum uric acid, diet, alcohol,
• Medications: diuretics, salicylates, B-blockers, PZA, ethambutol, Cyclosporin, tacrolimus, Insulin
GOUT

• ACUTE GOUT
  – First attack 4th-6th decade for men
  – Women almost always postmenopausal
  – Classically monoarticular – podagra (50%),
  – Proximal joint, central arthropathy uncommon
ALLOPURINOL

ALLOXANTHINE

RNA, DNA

Purines

Hypoxanthine

Xanthine oxidase

FEBUXOSTAT

Xanthine oxidase

Xanthine

URIC ACID

Blood

Excretion

Uric acid

PROBENECID

PROBENECID OR BENZBROMARONE

If Hyperuricaemia

Production of lysosomal enzymes (more joint destruction)

Potion of urate cryst. in synovial fluid

INDOMETHACIN

Colchicine

Release of lactic acid (more acidic pH)

Release of glycoprotein

Phagocytosis of urate crystals

(Inhibits release of glycoprotein)
Intercritical Period

• 70% prevalence of MSU crystals remain in the joint
• Lasts months to years for 75-80%, 20% never have another attack
Uric Acid Lowering Therapy

• Lifestyle, dietary modification
• Diet high in vegetables, dairy, water beneficial
• Initiate uric acid lowering therapy after 1(?) or 2 episodes of acute gouty arthritis
• Always prophylaxis for first 6 months with low dose steroids, NSAIDs, or colchicine
Treatment of Acute gout: Colchicine

• MOA: binds to tubulin & causes depolymer. & disapp of microtubules in granulocytes thus inhibiting granulocyte migration to inflamed jnt and phagocytosis.

• 2) inhibiting release of glycoprotein which aggravates inflamm by forming lactic acid & releases lysosomal enz.

Also stimulates gut motility.
ACUTE GOUT

If Hyperuricaemia

PROBENECID OR BENZBROMARONE

INDOMETHACIN

Production of lysosomal enzymes (more joint destruction)

Potion of urate cryst. in synovial fluid

Inflammation due to release of chemotactic factor

COLCHICINE (prevents infiltration)

Infiltration of granulocytes into the joint

COLCHICINE Phagocytosis of urate crystals

Release of lactic acid (more acidic pH)

COLCHICINE

Release of glycoprotein

(Colchicine inhibits release of glycoprotein)
Colchicine ...

- **Use**: Terminating acute attack – 0.6-1.2 mg --- 0.6 mg q 3hrly PO or IV --. Prophylactic 0.6mg TDS. Also used in Prim biliary cirrh., medit fever, sarcoid arthritis
- **A/E**: diarrhoea- m. common, N,V Abd pain. Chr toxicity- BMD, periph neuro, myopathy
Acute gout...

• **NSAIDS**: indomethacin- 50 mg q 6hrs --- reduced to 25mg q6-8hrly for 5days. Better tolerated than colchicine. Others ---except aspirin ,salicylates , tolmetin

• **Corticosteroids** : intraarticular preferred. Systemic CS reserved for refractory cases. # Prednisolone
CHRONIC TOPHACEOUS GOUT
Treatment of Chronic tophaceous gout

- **Allopurinol.** MOA: xanthine oxidase inhibitor; allopurinol itself competitive inhibitor (short act), major metabolite alloxanthine: long acting non-competitive inhib—mainly responsible for UA synth inhib. Deposition of urate crystals in ts –tophi- reversed & renal stone form inhibited

- Use: long acting, given 100mg OD----upto 300mg/d. to reduce UA levels < 6mg% 1) Used in chr tophaceous gout & gouty nephropathy.
Allopurinol… uses..

2) In recurrent urate stones.
3) Sec hyperuricemia d/t Ca chemo, radiation
4) during trt of myeloprolif dis like CML, AML
5) as adjuvant in kala azar
Allopurinol...

- A/E: ppt of ac attack during initiation of therapy-NSAID cover reqd. Hypersensitivity rxn, GIT, periph neuritis, cataract
- DI: Allo reduces metab of 6-MP & azathioprine ---so reduce their doses to 1/4th. Also enhances effects of cyclophosphamide.
- Potentiates axn of Oral anticoag & theophylline.
- Interferes with mobiliz of hepatic iron stores – avoid hematinics during therapy
Chronic gout...

• **Febuxostat**: 1st non-purine sel. inhib of XO oxidase, FDA approved 2009

• **PK**: > 80% abs PO. Extensively metab in liver – exc in urine.

• **Use**: 40, 80/120mg /d febuxostat more effective than allopurinol in lowering UA levels for trt of chr gout( intercritical pd ).

• **A/E**: as with allopurinol prophylactic NSAID/Colchicine reqd at beginning of trt. Liver fnct abn., D, H, N.
• PEGLOTICASE:
• pegylated modified porcine rt uricase
• FDA approved 2010 for chr gout refractory to conventional trt.
• Given by IV inf
Uricosuric agents

• Useful in under secretors Of UA
• Probenicid: not analgesic or antiinflamm- acts by promoting excretion of uric acid by inhibit its active reabsorp from renal tubules.
• Use – chronic gout, given with plenty of water & urinary alkaliser to prevent form of urate stone. Given Under NSAID cover. Dose 500mg/d.
• Also prolongs action of Pn/CS in gonorrhoea, SABE
Probenicid....

• A/E : GIT, allergic dermatitis; Nephrotic synd, convulsions in toxic doses
• DI : aspirin blocks uricosuric axn; probenicid inhibits urin exc of Pn, CS, methotrexate, indo-increases effect. It decreases effect of NFT in urine by inhibit tub. sec. into urine
Uricosurics ....

- **Sulfinpyrazone**: 
  - Str related to phenylbutazone. In therapeutic doses prevents reabsorp of UA from renal tubules.
  - **Use**: 100-200mg/d PO increasing over 2 weeks to 600mg/d – N uric acid levels – reduced to 200mg/d maint. Hydration imp. Effect additive with probenicid, blocked by salicylates
  - **A/E**: mainly GIT
  - **Cl**: peptic ulcer.
Uricosurics...

• Benzbromarone:
  • Newer, potent uricosuric, can be used in pts allergic or refractory to probenicid/sulfin or in pts with renal insuff.
  • Reversible inhib of tubular reabs of UA. Dose 60-80mg/d. Axn antagonised with sulfin or salicylates.
  • A/E –mainly git.