OSTEOARTHRITIS

- Chronic condition of articular cartilage degeneration — affect bones, cause pain, decrease functioning & even disability
- affect middle-age & elderly due to ↓se in strength of Tendons (bone-muscle) and ligaments and muscle and ↓se in proliferation of chondrocytes (component of cartilage — produce proteoglycans and collagen) and apoptosis

***SYMPTOMS:** deep, localized pain in joints
- pain & stiffness occur ē rest or immobility and last < 30min
- popping & cracking noise in joints upon moving
- affect — hips, knees, spine, feet & hands.

ETIOLOGIC FACTOR:

- advanced age, femal gender >55yr
- Muscle weakness, obesity, joint trauma develop. anatom. defect and repititive stress

Management:-

- Exercise & reduction in wt
- Acupuncture
- Thermal Therapy (hot shower, ice pack).

Pharmacologic:

- Acetaminophen — 1st line.
- NSAIDS or COX-2 inhibitor (celecoxib) — 2nd line.
- Tramadol — 3rd line for pain.
- Opiate analgesic (codeine, oxycodone) — 4th line
- Topical analgesic (use as monotherapy for pain or in comb. ē others)
  - ✓ Capsaicin — ↓se sub. P, pt should wash hand after applying to avoid burning in other areas.
  - ✓ Diclofenac (voltaren gel)
- Intra-articular injections (corticosteroids)
- Chondroitin — protect again collagen breakdown

Rheumatoid Arthritis

- chronic, systemic autoimmune disease that involve inflammation in membrane lining of joints & often affect internal organs.

★ SYMPTOMS

⇨ In early disease: malaise and anorexia, symmetrically tender & swollen joints
- pain in joints
- Affect metatarsophalangeal (MTP) & wrist
- Other areas include spine, shoulder, ankle & hip.
- Inflammed SYNOVIUM is a HALLMARK of RA

★ ETIOLOGY:

infection, or trauma are Thought to trigger RA. ↓ modify autoantigens
- genetics. Smoking → autoimmune

★ MANAGEMENT:

- When a pt diagnosed ē RA DMARDS should be started ein 3 months to help stop Progression. NSAID/corticosteroid may be use for symptomatic relief.

⇨ Low disease activity: Monotherapy ē DMARD

⇨ moderate — severe Disease. Combination DMARD Therapy usually MTX based or use of anti-TNF

⇨ Pt ē more establis. disease use of other biologic therapies (abatacept, rituximab)

★ - most of these agents are (PG)

Rheumatoid Arthritis

- Related to muscle & skeletal system — Arthra → Joints; itis → suffix for inflammation
- autoimmune disorder
- Involve synovium & tissue adjacent to synovium

ETIOLOGY

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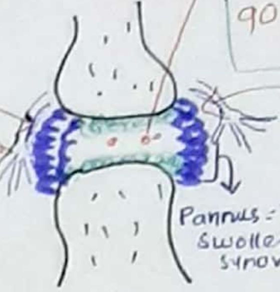
- Immunologic factor
  - HLA-DRB1 (Human leukocyte antigen) → keep → locus: chrom-6
  - encodes for AA sequence
  - The proteins produce from this gene help immune sys. to disting. b/w self & non-self cells
- Other
  - menopause, preg, Oral contrac
  - smoking, infection

⇒ Pathophysiology:

- articular cartilage (bone cover for easy ...)
- Synovial membrane (synovium) joint lining
- fibrous layer

- Synovium cell start proliferating → Pannus formation
- ⊕ → Fibroblast like synoviocyte proliferate → RANKL-expression → Osteoclast activa → bone ⊖
- TNF-α, IL-1, IL-6 ↑ ⊕ → Proteases → cartilage breakdown
- activate macrophage ← recruit ← cytokines ⇄ IF-γ, IL-17



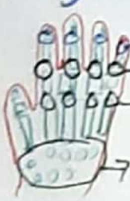
- Autoantibody → Rheumatoid factor IgM; Anti-citrullinated antibody
- 90 in synovium & fights against our body → autoantibody ↑ plasma cells ↑ proliferate ↑ B cell activ

- Due to etiologic factor, structure collagen proteins modify along ē vimentin present in synovium ⇒ immune cell that provide protection to synovium, consider new protein as antigen → T-cell activate → B cell activ
  - ⇓
- Arginine A·A → (replace/convert) citrulline (citrullination)
- ⚬⚬ RANKL: receptor activator of nuclear factor kappa-B ligand (release by osteoblast to prep osteoclast)
- By these antibodies we can identify whether the person is suffering from R·A or not. These antibodies can also form complex ē each other causing more inflamm. → angiogenesis → ↑↑ inflammation
- Collagen present in other body parts, skin, myocardium, etc also show deformaties. (Non-articular features)

CLINICAL SIGNS

Most common Joints (occur in osteoarthr. DIP)

- Small Joints
  - MCP (metacarpophalangeal)
  - PIP (proximal interphalangeal)
  - MTP (metatarsophalangeal) (like joints wrist joint) in feet
- Pain, swelling, stiffness



Specific deformities

- distal interphalangeal joint — DIP Flex; PIP Hyper exten

- Swan-Neck deformity
- Button hole deformity → opposite to swan neck
- cock-up Toe defor
- ULNAR Deviation — MCP joint swollen & cause fingers to bent toward little finger

INFLAMMATION IN RHEUMATOID ARTHRITIS

- Normally the immune system can differentiate b/w self & non-self.
- In R/A, WBCs view Synovium (synovial membrane) (tissue that nourishes cartilage & bone) as non-self and initiate inflammatory attack → Synovitis
  - Bone & cartilage erosion
  - Angiogenesis
- ∴ Etiologic factors → modify autoantigen (our own antigen seems foreign to our immune system) → WBCs activation
- Inflamm → modify autoantig → Stimulation of T-Lymphocytes (in Lymph nodes)
- Recognize by antigen presenting cells (which recruit and activate monocytes & macropha)

↓

These cells secrete proinflammatory cytokines (TNF & IL-1) into Synovial cavity, which causes (IL-6)

① increased cellular infiltration into endothelium due to release of histamines, kinins & vasodil. prostaglandins

② increased produc. of C-reactive protein (CRP) by hepatocytes (a marker for inflammation).

③ increased production and release of proteolytic enzymes (that breakdown) by chondrocytes (cell that main cartil) leading of degradation of cartilage & joint space narrowing

④ increased osteoclast activity (that regulate bone breakdown)

↓

- Focal bone erosion
- Bone demineralization around the joint

⑤ Systemic manifestation in certain organs such as ✓ Atherogenesis

- Neurologic → ✓ Fatigue, ✓ Depression
- Heart → ✓ MI, ✓ Stroke
- Skin → Nodule form
- Liver → ↑CRP, ↑ESR, ↑ Hepcidin → Anemia
- Osteopenia → Osteoporosis
- Muscle → Insulin resistance

★ In addition to T-Lymphocytes, B-lymp are also involved & produce rheumatoid factor (inflammatory marker) (IgM → form immune complexes) and other autoantibodies ē purpose of maintaining inflammation

e.g. anticitrullinated protein antibody (more common)

↓

These defensive reaction cause progressive tissue injury

↓

JOINT DAMAGE AND EROSIN, FUNCTIONAL DISABILITY
SIGNIFICANT PAIN AND REDUCTION IN QOL

MANAGEMENT:- Includes Anti-inflammatory & / or immunosuppre. agents.

- RANK-Ligand (RANK-L): membrane protein & is member of Tumor Necrosis Factor superfamily → Function → {regulate Osteo-clast-actin}

DMARDS (MTX)

- Mainstay treatment → RA & psoriatic arthritis
  (form of arthritis that affect people suffering from psoriasis — red patches appear on skin & silvery scales)
- Folic acid Antagonist → inhibit cytokine produc → purine biosynthesis
  Slow appearance of erosin in involved joints ↑
  Immunosuppressive & anti-inflammatory
- Response start within 3–6 week of starting
- Partial / No response = Add other DMARD with MTX
- Dose for RA < Dose for chemo
  ↓ once /week — DI → Penecillin, NSAID, cyclospori

Side effects: Mucosal ulceration & Nausea. Cytopenias (↓se in no. of mature blood cells particularly WBCs), cirrhosis and acute pneumonia-like syn → with chronic adm) (PG)

⇨ leucovorin (folinic acid) OD after MTX ↓se ADRs

⇨ Recommended Test: LFT, CBC, signs of infection

★- LEFLUNOMIDE :-

Causes cell arrest of autoimmune lymphocytes through its action on Dihydroorotate dehydrogenase — role in pyrimidine biosynthesis (DHODH)

Dihydroorotate —(DHODH ⊖)→ Orotate → → monophos uridines → RNA ⊖

- can be use alone or in combo with MTX
- Headache ; N/V/D . wt. loss, allergic rex and hypokalemia

(Liver Dise) — as it ↑se hepatotoxicity

- Monitor sign of infection, CBC & liver enzymes

∴ Purine = Adenine & Guanine
Pyrimidine : Cytosin & Thymidine (uracil in RNA).

HYDROXYCHLOROQUINE

- use for early & mild RA
- often in comb with RA • Take with food.
- Also use in treatment of Lupus & malaria. (DI ↓ cimetidi)

⇨ MOA = unknown (↓TNFα, IL1B)

★ ONSET = 6 week → 6 months

- has less effect on liver & immune sys. than other DMARDs
- Cause OCCULAR-TOXICITY
  ⇓
  irreversible retinal damage & corneal deposits (fine golden-brown or gray deposits)
- CNS depression, GI upset & skin discoloration & eruptions.

★-MINOCYCLINE :- Tetracycline

antibiotic — NOT First line for RA

- can be use alone or in comb. with other DMARDs, as it has been shown to be effective against R.A. (DI — Ca^{2+}, Mg^{2+}, Al^{3+}, Fe)

★ Sulfasalazine : For early, mild R.A in combin with MTX and/or Hydroxychloroquine

(DI: Ss ↑se warfarin, ↓se Fe, Digoxin (↓se digoxin absorp), ↓se S.S absorb)

ONSET — 1–3 months

- leukopenia (Sulfonamide)
- MOA — in RA = unclear.
  ∴ some consider this as 1st line.

★ Glucocorticoids :-

Potent anti-inflamm. drugs

↓ provide symptom. relief

↓ bridge the time until DMARDs are effective

- Timely dose-reduc & cessation are necessary = ↓ADRs with long term used

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BIOLOGIC THERAPIES IN R.A

IL-1 & TNF-α (pro-inflamm. cytokines) → Stimulate synovial cell to proliferate & synsthes. collagenase → degrade cartilage

↑ secreted

Synovial macrophages

- Stimulate bone resporption
- Use proteoglycan synthesis

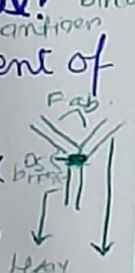
- clinical response can be seen ēin 2 weeks
- ē DMARDs — The decision to continue or stop. a b. therapy can be made within 3 months after initiation of Therapy
- If one TNF-α inhibitor FAILED → use Diff. TNF-α-Inhs (or) → Non-TNF biolo. therapy
- TNF-α Inhib NOT to be use ē Non-TNF-α → due to ↑se risk of infecti
  - Tb & sepsis, fungal oppert infec & pancytopenia → Are the Risk
  - (CI) — ē Live vaccination, HF, Risk of lymphom & other cancer

★-ADALIMUMAB:-

- Recombinant monoclonal antibody
- Binds to TNF-α (−) Binding of TNF-α to cell surface receptor
- Indicated for moderate → severe R.A
  - Either as monotherapy or combē MTX
- Also indicated for psoriatic arthritis, ankylosing spondylitis & Crohn's dis.
- Adm S/C /week or every other week
- Headache, Nausea, Agranulocytosis, ↑se risk of (UTI, URTI & sinusitis)

★-Certolizumab pegol:

- TNF-α blocker ē Fab fragment of humanised antibody
- Potent neutralizer of TNF-α
- Combination product ē PEG
- S/C q 2 week
- Indic — same as Adalim
- ADRs - similar to other TNF-α Inh.



★-ETANERCEPT: genetically engi

Soluble, recombi, fully human recep. fusion protein BINDS → TNF-α (−) Binding to recepto

- For mode → severe RA, ē or ē of MTX
- Also for anky. spon. & psoriasis
- combin. of MTX & entanercep > both alone. effective
- S/C Twice a week.
- well Tolerated. ē other TNF-α-Inhib ↓ ↑HF & ↑se risk of infec.

★-GOLIMUMAB:-

- Bind to TNF-α
- S/C — once a month, in combē MTX or other DMARS
- ↑se hepatic enzymes
- Reactivation of hep-B in chronic carriers
- ē other TNF-α In. → ↑se infec risk.