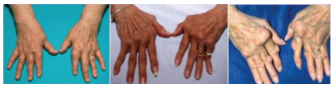
PHAR3826 Notes – Musculoskeletal, Dermatological and Senses

Rheumatic diseases

- Unknown trigger activates lymphocytes to produce inflammatory cytokines
- Autoimmune diseases – higher cardiovascular risk and mortality, require preventative therapy
    - Rheumatoid arthritis – 3x higher mortality rate due to CVD
    - Psoriasis – independent CVD risk factor
- Rheumatic diseases associated with high TNF (and interleukin) levels:
    - Rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, juvenile chronic arthritis
- ~100 forms of arthritis – osteoarthritis, RA, juvenile arthritis, gout, ankylosing spondylitis, lupus

Rheumatoid arthritis (RA)

- Chronic, systemic inflammatory autoimmune disease with localised and general manifestations
- Polyarticular synovitis → pain, swelling, joint stiffness of hands/wrists/feet, joint destruction
- Coexisting conditions (due to excess TNF and IL-1/6)
    - Vascular disease – ischaemic heart disease, vascular dementia, atheroma
    - Metabolic syndrome, insulin resistance
    - Cognitive dysfunction and depression
    - Osteoporosis, disability, functional limitations



- 15-70% of the risk of developing RA may be due to genetic factors

Pathology

1. Inflammatory cytokines cause proliferation of connective tissue
2. Synovial cells proliferate, then invade and destroy cartilage and bone by:
    - Producing IgG – attracts leukocytes which secrete hydrolases that degrade collagen
    - Causing inflammation – elevated prostanoids, joint swelling, low grade fever, pain

Treatment

- Prior to treatment – baseline assessment, CVD risk, consequences of immune suppression
    - Early referral to rheumatologist improves outcomes and reduces disease progression
        - Note: many diagnosed patients rely solely on OTC therapy – intervention required
- Aims of drug therapy – symptom relief, prevent (further) damage to bones/joints/organs
    - No evidence for clinical superiority amongst anti-rheumatics
    - Avoid live vaccines with immunosuppressants, attenuated vaccines are okay
- Drugs – analgesics, monoclonal antibodies, methotrexate, prednisolone, hydroxychloroquine
    - bDMARDs – biological disease modifying anti-rheumatic drugs
        - TNF-inhibitors – e.g. adalimumab, etanercept (*very expensive)
            - Increasing intervals between injections to taper dose appears effective
    - Oral steroids – effective, fast acting, use lowest dose for shortest duration

Stage	**Treatment options**
Mild	Sulfasalazine, hydroxychloroquine, steroids
Moderate –severe	Low-dose methotrexate ± MAB/leflunomide; or combination DMARDs; IM gold
Severe joint damage	Orthopaedic surgery – total joint arthroplasty
Supplement	2.7g/day omega 3 fatty acids may reduce symptom severity

Psoriasis

- Autoimmune disease – chronic, recurrent, benign (cosmetic issue)
    - Plaques of the skin, scales, erythema, dryness, blisters, broken skin may lead to infection
    - Usually affects front of knees, back of elbows – often *symmetrical*
- Nail psoriasis – swollen fingers, raised nails, nail crumbling and pitting, white discolouration
- Two peaks of onset – 16-22yo (more severe disease) and 57-60yo (milder)
    - Strongly familial
- Triggers – infection, stress, skin trauma (sunburn, scratches), drugs (β-blockers, ACEI, lithium)
- 30% develop psoriatic arthritis
- Eczema = dermatitis ≠ psoriasis

Pathology and histology

- Dysregulation in production of skin – build-up of excess skin cells (growing too fast)
    - Keratinocyte *hyper*proliferation + *hypo*differentiation
    - Inflammatory cell infiltrates
    - Dermal papillary blood vessel changes (redness)
- Elevated interleukin-17 and interleukin-22/23 (produced from T_H-17/22/23)
    - Mediate production of chemokines and subsequent neutrophil recruitment

Treatment

- Information gathering questions – duration of symptoms, treatments already tried, family history
- Treatment can control the disease in most cases, but are *not curative* due to backsliding
- Tar and dithranol – messy, unpleasant odour, stains skin and clothes

Topical therapy	**Mechanism of action**
Emollients, moisturisers	Relieves scaling and irritation, improves appearance, loosens flaky skin
Keratolytic (salicylic acid)	Removes loose scales
Corticosteroids	Anti-inflammatory, anti-mitotic
Coal tars	Anti-inflammatory, anti-pruritic, slows rapid turnover of skin cells
Vitamin D analogues	Calcipotriol/dithranol – ↓ keratinocyte proliferation and differentiation
Systemic therapy	**Mechanism of action**
Acitretin	↓ Keratinocyte proliferation and differentiation, anti-inflammatory
Apremilast	PDE_4 inhibitor – ↓TNF-α and IL-17/23
Adalimumab (biological)	For moderate-severe chronic plaque psoriasis (3-12 weeks for effect)
Cyclosporin, methotrexate	Immunosuppressant, slows epidermal cell proliferation
Phototherapy	Anti-inflammatory, causes epidermal remodelling

Topical corticosteroids

- Glucocorticoids inhibit release of IL-1/2/6 and TNF-α by dendritic cells and macrophages
    - Mild corticosteroid (S3) – 30g hydrocortisone 1%
    - Moderate (S4) – 2x 100g triamcinolone 0.02% or betamethasone 0.02%
    - Strong (S4) – 15g or 10-20x 15g tubes (authority script), avoid if <18yo
- Avoid using mild-moderate steroids continuously on skin – tolerance with >3 weeks
    - Use short-term then cease, or 1 day on and 1 day off, or weekdays on and weekends off
- Long-term strong steroids – thins skin, skin atrophy, systemic side effects with extensive use
- Consider treatment rotation if tolerance develops – e.g. steroids ↔ tar ↔ dithranol

Type of psoriasis	**OTC**
Plaque (mild/mod)	Coal tars, topical corticosteroids, calcipotriol, dithranol
Flexural (skin folds, genitals), facial	Mild-moderate topical corticosteroids (short-term only)
Palmoplantar (palms, feet soles)	Coal tars, topical corticosteroids, keratolytics, systemic therapy
Scalp	Tar shampoo + emollient, topical corticosteroid lotions

Psoriatic arthritis

- Involves hands, feet, spine, sacroiliac joints, peripheral joints – possible joint damage
    - Symptoms vary in severity, often undergo bouts of flares and remissions
- Psoriasis symptoms usually precede joint symptoms (arthritis) in >80% patients, often by 10 years
    - Severity of skin disease does *not* correlate with severity of psoriatic arthritis
- Usually affects young to middle-aged adults
- Distinguishing characteristics not present in rheumatoid arthritis:
    - Psoriatic plaques
    - Negative rheumatoid factor
    - Dactylitis (inflamed digits) and enthesitis
    - Proliferative bone changes, distal interphalangeal joint involvement, asymmetric arthritis
- Treatment – oral NSAIDs, oral corticosteroids, DMARDs, TNF-α inhibitors

Opioid analgesics

Pain sensation

- Pain manifestation or nociception – recognition of pain stimuli (pressure, heat, chemicals)
- Endorphins and opioid receptors – associated with transmission of pain signals
    - Occur in dorsal horn (spinal cord), thalamus and periaqueductal gray
- Analgesics act centrally to increase capacity for pain – ↓ ability to interpret, integrate and react

Non-narcotic analgesics	**Narcotic analgesics**
Effective for sharp, localised, non-visceral pain	Effective for duller, chronic, intense, less localised pain
Peripheral and central mechanisms	Modify effects of pain impulses on the CNS

Central effects	**Other effects**
Analgesia – for dull, continuous, severe pain	GI tract: ↓ motility + ↑ tone = constipation
Euphoria and sedation	Histamine release – itching
CNS depression – CV and respiratory centres	**Therapeutic applications**
Affects cough reflex (antitussive)	Analgesia
Nausea	Sedation and anti-anxiolytic
Tolerance and dependence	Antitussive and diarrhoea
Miosis – pupillary constriction	Antagonism of opioid toxicity

Tolerance	Increasing doses needed to achieve same effect
Physical dependence	Drug must be continued to maintain "normal function" (i.e. prevent withdrawal)
Withdrawal symptoms	- Anorexia, weight loss, vomiting, nausea, chills, sweating, tachycardia - Abdominal cramps, muscle spasm, hyperirritability - Lachrymation, rhinorrhoea, gooseflesh, pupillary dilation

Endogenous opioids

- Three groups of peptides that affect opioid receptors
    - Endorphins – β-endorphin
    - Enkephalins – met-enkephalin, leu-enkephalin
    - Dynorphins

Endogenous precursor protein	**Resultant endogenous opioids (via proteases)**
Pro-opiomelanocortin (POMC)	β-endorphin, melanocyte stimulating hormones, lipotropins
Pro-enkephalin A	Met- and leu-enkephalins (found both in CNS and periphery)
Pro-enkephalin B	Dynorphins A and B

Opioid receptors

- All opioid receptors are GPCRs – affect second messenger systems, and K^+ and Ca^{2+} channels
- Three receptor types – μ, κ, δ
    - μ1 (high affinity for morphine), μ2 (low), κ1 (high), κ2 and κ3 receptors
- μ shows strongest effects (analgesia, respiratory depression, euphoria, sedation, dependence)
- Pro-opioid protein → processed via peptidases into enkephalins → action potential fires → enkephalins released into synapse → bind and activate opioid receptors on post-synaptic cell
    - μ-receptor is mediated via $G_{i/o}$-protein
        - Inhibits adenylate cyclase → ↓cAMP
        - Activates K^+ ion channels → K^+ efflux → hyperpolarisation → cell stops firing
    - Degraded by enkephalinases – flanks peptides between Gly-Phe
- Naloxone – opioid antagonist, stops exo/endogenous opioids from binding receptor
- Search for non-addictive analgesics
    - Pentazocine – weak partial agonist at μ, agonist at κ (dysphoric rather than euphoric)

Endogenous	**Receptor selectivity**	**Exogenous**	**Receptor selectivity**
β-endorphins	Non-selective	Morphine	μ 20x > κ and δ
Dynorphins	κ only – dysphoria	Sulfentanil	μ 100x > κ and δ
Enkephalins	μ and δ – euphoria	Nalorphine	Agonist at κ; antagonist at μ