Unit IX – Problem 4 – Pharmacology: SLE-Principles of Management

- **Introduction to the disease (SLE):**
  - What is SLE? → it is a chronic autoimmune disease which occurs more in females - 90% of them are in their childbearing age- and characterized by various manifestations –triggered by genetic and environmental factors- with flare-ups and remissions.
  - Lupus can also be induced by many drugs.
  - The most important lab investigation: positive ANA (antinuclear antibody).
  - Management of this diseases is divided into: conservative therapy (lifestyle management) + drug therapy.
- **What are the goals behind treating/ managing SLE?**
  - To prevent flare-ups + reducing its severity and duration.
  - To achieve remission rather than cure.
  - To control pain and inflammation + suppressing immune reaction.
  - To manage organ-specific complication (such as glomerulonephritis in the kidney).
- **What are the drugs which are used to treat/manage SLE?**
  - **NSAIDs (Non-Steroidal Antinflammatory Drugs):**
    - ✓ Properties:
      - ❖ *Reducing pain and inflammation*: ibuprofen and naproxen.
      - ❖ *Reducing pain only*: acetaminophen.
    - ✓ NSAIDs can act centrally or peripherally.
    - ✓ Mechanism of action: inhibition of cyclooxygenase enzyme thus decreasing the formation of prostaglandins:
      - ❖ *Non-selective*: inhibiting both COX-1 and COX-2.
      - ❖ *Selective*: inhibiting COX-2.
    - ✓ Remember that NSAIDs are used to control pain and inflammation in (arthritis: inflammation of the joints).
    - ✓ Adverse effects include the following:
      - ❖ *GI disturbance (most common with non-selective NSAIDs).*
      - ❖ Increased risk of: aseptic meningitis (meningitis which is not caused by bacteria), elevated serum transaminases, cardiovascular and renal dysfunctions.
      - ❖ Salicylates: ototoxicity (toxic effect to the ear) and tinnitus (buzzing in the ear).
  - **Hydroxychloroquine:**
    - ✓ It is a drug which is used to treat malaria (anti-malarial drug).
    - ✓ Effects of the drug: it controls the following:
      - ❖ Dermatitis (skin lesions).
      - ❖ Arthritis.
      - ❖ Fatigue.
    - ✓ Mechanism of action: suppression of immunity through the following:
      - ❖ Interferes with processing and presentation of antigens.
      - ❖ Interferes with production of cytokines.
      - ❖ Inhibits chemotaxis of neutrophils and eosinophils.
      - ❖ Impairs complement-dependent antigen-antibody reactions.
    - ✓ Adverse effects:
      - ❖ *Agranulocytosis*: severe and dangerous leucopenia most commonly of neutrophils thus predisposing the patient to serious infections (due to suppressed immunity).
      - ❖ *Retinopathy*.
  - **Glucocorticoids:**
    - ✓ They are commonly used in combination with NSAIDs.
    - ✓ Relation of route of administration with effect of the drug:

- ❖ *Topical (for dermatitis):* triamcinolone and hydrocortisone.
- ❖ *Oral (for systemic effect):* prednisone and prednisolone. Indications for using prednisone include the following:
  - ➢ CNS involvement.
  - ➢ Renal involvement.
  - ➢ Severely ill patients without CNS involvement.
  - ➢ Hemolytic crisis.
  - ➢ Thrombocytopenia.
- ❖ *IV (for severe life-threatening SLE):* methyprednisolone.

✓ Mechanism of action: decrease inflammation by suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability. Glucocorticoids are immunosuppressive and anti-inflammatory.

✓ Adverse effects:

- ❖ Opportunistic infections (due to suppression of immunity), iatrogenic Cushing's syndrome (drug-induced) and suppression of the pituitary-adrenal axis.
- ❖ Alternate-day therapy minimizes the adverse effects.

- **Immunosuppressants:**

Antimetabolite (azathioprine)	• Used with standard treatment of severe cases • Mechanism of action: antagonizes purine metabolism thus inhibiting the synthesis of DNA, RNA and proteins + interfering with cellular metabolism and inhibiting mitosis (especially proliferation of T-cells, B-cells and macrophages).
Alkylating agent (cyclophosphamide)	• Slowing the progression of end-stage renal disease (ESRD) • It is a prodrug which must be metabolized to active metabolites in the liver. • Mechanism of action: preventing cells division by cross-linking DNA strands and decreasing DNA synthesis. • Effects: suppression of both cellular and humoral immunity + anti-inflammatory effect.
Antimetabolite (methotrexate)	• Used for severe arthritis/ dermatitis • Mechanism of action: folate antimetabolite which inhibits the formation of reduced folates and thymidylate synthetase thus resulting in inhibition of purine and thymidylic acid synthesis. • Effects: suppression of both cellular and humoral immunity + anti-inflammatory effect.
Purine synthesis inhibitor (mycophenolic acid)	• Used with standard treatment of severe cases • Mechanism of action: inhibition of inosine monophosphate dehydrogenase (IMPDH) which inhibits de novo guanosine nucleotide synthesis thus reducing proliferation of T and B lymphocytes.

- **Monoclonal antibodies:**

✓ Use: they are given IV for severe organ involvement.

Belimumab	• IgG1-lambda monoclonal antibody. • Mechanism of action: preventing the survival of B-lymphocytes by blocking the binding of soluble human B-lymphocyte stimulator protein (BLyS) to receptors on B-lymphocytes. • Onset of action: ✓ B-cells: 8 weeks. ✓ Clinical improvement: 16 weeks.
Retuximab	• Mechanism of action: directed against CD20 antigen on B-lymphocytes thus activating: ✓ Complement-dependent B-cell cytotoxicity.

	✓ Antibody-dependent cellular toxicity. ✓ Direct lysis by natural killer cells.

- **Lifestyle modifications to manage SLE:**
  - Avoidance/ protection from sunlight.
  - Regular exercise
  - Sufficient rest.
  - Healthy diet.
  - Smoking cessation.
  - Taking calcium, vitamin-D and bisphosphonates.
- **Comparison between non-life threatening SLE and life-threatening SLE:**

Non-life threatening SLE	Life-threatening SLE
• Fatigue, pain and autoantibodies of SLE (with no major organ involvement). • Mainstay (الدعامة الأساسية): analgesics (NSAIDs and acetaminophen) and antimalrials. Notice that topical steroids or those with low oral dose can be used.	• Mainstay: systemic glucocorticoids and methylprednisolone sodium succinate IV

- **Pregnancy and SLE:**
  - There is a placental enzyme which deactivates glucocorticoids: it is more effective in deactivating prednisone and prednisolone than the fluorinated glucocorticoids dexamethasone and betamethasone.
  - **FDA pregnancy categories:**

Category	Description	Drugs for SLE
A	No risk in controlled human studies	• Glucocorticoids
B	No risk in other studies	-
C	Risk not ruled out	• Cyclosporine • Tacrolimus • Rituximab
D	Positive evidence of risk	• Azathioprine • Hydroxychloroquine • Mycophenolate mofetil • Cyclophosphamide
X	Contraindicated in pregnancy	• Methotrexate
N	Not yet classified	-

  - Therefore, active SLE in pregnant women should be controlled with prednisone/prednisolone at the lowest effective doses for the shortest time required.
  - **Effects of glucocorticoids on the baby:**
    - ✓ Low birth weight.
    - ✓ Developmental abnormalities in the CNS.
    - ✓ Predilection toward (الميل والنزوع إلى) adult metabolic syndrome.
  - Patients should consider not breast-feeding if they need therapy for SLE.
- **Prevention of SLE**: it may not be preventable but its complications are preventable:
  - **Vaccination** (pneumococcal and influenza).
  - **Calcium and vitamin-D** to prevent osteoporosis which results from the use of glucocorticoids.
  - Use of **sunscreens** (to avoid sunlight).
  - **Slowing atherosclerosis** due to vasculitis.