PASSION ACADEMIC TEAM

YU - MEDICINE

MUSCULOSKELETAL SYSTEM

Sheet#3 - Pharmacology

Lec. Title : Rheumatoid Arthritis (Part 2)

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Rheumatoid arthritis

- This lecture will mainly discuss the types of DMARDs which divide into 3 types:

1. traditional nonbiologic DMARDs
   - Methotrexate
   - Hydroxychloroquine
   - Sulfasalazine
   - Leflunomide

2. biologic DMARDs
   - TNF antagonists
   - IL-1 antagonists
   - Costimulation modulators
   - Anti-CD20 monoclonal antibody
   - IL-6 antagonists

3. Janus-kinase inhibitors
   - Tofacitinib.

❖traditional nonbiologic DMARDs:

- **Methotrexate:** first line of choice.
  - Methotrexate is the nonbiologic DMARD of choice in RA because of its documented efficacy and safety profile when monitored appropriately.

  - MOA: Methotrexate exerts its anti-inflammatory effect through inhibition of dihydrofolate reductase, which causes inhibition of purines and thymidylic acid, and by inhibiting production of certain cytokines.

  - Rule of administration: orally if GI problems occur it's given IM or S.C

- Dosage frequency : 1 dose **weekly**

- Onset of action: 4-8 weeks

- adverse effects include:
    1. Alopecia.
    2. Cough or SOB (shortness of breath).
    3. Stomatitis, diarrhea, nausea.
    4. Myelosuppression (a bone marrow suppression that causes infection and anemia).
    5. Elevated liver function tests.

- Concomitant folic acid is given routinely to reduce the risk of folate-depleting reactions induced by methotrexate therapy. **(leucovorin)**

- Contraindicated in pregnancy because it's associated with spontaneous abortion, fetal myelosuppression, limb defects, and CNS abnormalities.

- If it doesn't produce resolution combine it with other nonbiologic or biologic DMARDs:
    - ✓ methotrexate with Hydroxychloroquine or sulfasalazine is good choice
    - ✓ With Leflunomide is not preferred because of the high hepatotoxicity.

- **Hydroxychloroquine and sulfasalazine:**
  - MOA: not known exactly
  - Fairly well tolerated agents.
  - Onset of action: slow(*8-24 weeks*)→ given at least 6 months.

    - **Hydroxychloroquine**:
      - ✓ Therapeutic use:
        - For patients with contraindications to other DMARDs because of their toxicities. (Because it's not associated with renal, hepatic, or bone marrow suppression).
        - For pregnant woman with RA.
      - ✓ Adverse effects: Nausea, diarrhea, headache, vision changes, skin pigmentation.

    - **Sulfasalazine:**
      - ✓ Adverse effects: diarrhea, rash, yellow-orange discoloration photosensitivity , myelosuppression, nausea and abdominal discomfort.
      - ✓ Start at low doses and titrate slowly to prevent GI problems.
      - ✓ Contraindicated in Patients with a sulfa allergy.
      - ✓ Could be given for pregnant woman with RA.
      - ✓ Other therapeutic use of sulfasalazine is in inflammatory bowel disease.

  - Sun cream is used to prevent skin pigmentation and yellow-orange discoloration that occur as an adverse effect of these two drugs.

- **Leflunomide:**
  - MOA: inhibits the T-lymphocyte response to various stimuli and halts the cell cycle by inhibiting dihydroorotate dehydrogenase, an enzyme within mitochondria that supplies T lymphocytes with the necessary components to respond to cytokine stimulation.

  - Onset of action: 4-12 weeks
  - Half-life is very long, reaches 10 days.
  - **Cholestyramine** is an antidote for it: accelerate leflunomide removal from the body.
  - Adverse effects: Hepatotoxicity, diarrhea, nausea, Hypertension, rash, headache, abdominal pain.
  - Contraindicated in pregnancy.

❖Biological DMARDs:

- They are produced from living cells, tissues or microorganisms.
- Indicated in patients who have received an adequate trial of nonbiologic DMARD monotherapy (methotrexate) or combination therapy (methotrexate with hydroxychloroquine, sulfasalazine or Leflunomide) but have failed to achieve treatment goals.
- They have a very specific target which increases their efficacy.
- These agents may:
  - ✓ Be added to nonbiologic DMARD monotherapy (eg, methotrexate)
  - ✓ Replace ineffective nonbiologic DMARD therapy
  - ✓ Be considered for initial therapy (based on current guidelines).
  - ✓ We don't prefer to use them from the beginning because of their high cost and they are given by injection rather than orally.

- Usually we start with TNF antagonist if it fails we move to the other biological factors.

- **Tumor necrosis factor (TNF) antagonists:**
  - There are currently five reference TNF antagonists approved for the treatment of RA:
    1. etanercept
    2. adalimumab
    3. infliximab
    4. golimumab
    5. Certolizumab

    *mab means that they are monoclonal antibodies.
  - Onset of action: 1-4 weeks (shorter than non-biologic)
  - Patients prescribed these agents should be screened for TB and hepatitis B and C. especially in patients with latent TB because they are immune suppressant agent.

  - If the screen shows an active TB the patient must get a full course of TB treatment, after that start with TNF antagonists.
  - If the screen shows a latent TB start with treatment of TB, after one month of treatment start with TNF antagonists.

  - At pregnancy:
    - ✓ TNF antagonists are considered safe in the first trimester.
    - ✓ Etanercept and certolizumab may be continued throughout the pregnancy because the transfer of medication across the placenta is very low.

1. **Etanercept**:

- Recombinant human T cell receptors that binds to soluble TNF.so, it will prevent TNF to attach with TNF receptors that located normally on the immune cells and that will inhibit the immune reaction amplifying.
- Route of administration: s.c.
- Therapeutic uses:
  - ✓ as monotherapy
  - ✓ In combination with other nonbiologic DMARDs.
  - ✓ Treatment of juvenile idiopathic arthritis (JIA).

- Adverse effects: injection site reactions
- To prevent the adverse effect→ treat with topical corticosteroids, antipruritics (anti-itch), analgesics, rotate injection sites.

2. Adalimumab:

- It is a recombinant human IgG1 monoclonal antibody specific for human TNF. That binds to soluble and bound TNF-α.
- Route of administration: s.c.
- Therapeutic uses:
  - ✓ In combination with methotrexate or other DMARDs
  - ✓ Treatment of juvenile idiopathic arthritis (JIA).
- Adverse effects: injection site reactions.

3. Infliximab:

- It is a chimeric IgG1 monoclonal antibody that binds to soluble and bound TNF-α.
- Chimeric means it's a mix between human and mouse antibodies.
- This combination has advantages and disadvantages.
  - ✓ Advantages: it's easier to produce them than human antibodies and they are lower in cost.

  - ✓ Disadvantages: presence of mouse antibodies can cause multiple problems:
    a) Antibodies production against the mouse-derived portion of the molecule, this will suppress the action of the drug.
    - You have to use methotrexate with it to suppress these antibodies production.

    b) Infusion-related reactions: during the infliximab infusion a hypersensitivity reaction my occur including: rash, urticaria, flushing, headache, fever, chills, nausea, tachycardia and dyspnea.
    - To prevent and treat the reaction :
    - Infliximab should be given at the hospital
    - Qualified health care personnel must be present.
    - Temporarily discontinuing the infusion.
    - Slowing the infusion rate.
    - Administering corticosteroids or antihistamines.
    - If the patient develop these reactions at the first time of infusion, and still continue to experience infusion reactions at the second time, at the third time the patients should be pretreated with corticosteroids or antihistamines.

يعني إذا أول جلسة بالعلاج ظهرت عنده أعراض الحساسية وعالجناه ورجع المرة الثانية طلعت عنده هي الأعراض بالجلسة الثالثة بنعطيه الأدوية المضادة للحساسية قبل الانفليكسيماب وما بنستنى لحتى تظهر الأعراض

4. Golimumab:

- Is a human monoclonal antibody that binds to membrane-bound and soluble TNF.
- Rout of administration :(One advantage of this agent over others in the class)
  - ✓ Once-monthly S.C. dosing.
  - ✓ Every-other-month IV dosing. (every two months)
- Therapeutic uses:
  - ✓ In combination with methotrexate in patients with moderate to severe RA.

5. Certolizumab:

- Humanized antibody Fab fragment conjugated to polyethylene glycol, which delays its metabolism and elimination→ then decreasing the frequency of administration.
- Explanation: a genetic modification on some portions of the antibodies to be like human ones (Humanized) to reduce the immune response to these foreign antibodies and then conjugation with polyethylene glycol.
- Therapeutic uses:
  - ✓ can be administered alone
  - ✓ in combination with methotrexate in patients with moderate to severe RA.

- **Interleukin-1 antagonists: (Anakinra)**
  - Recombinant form of human IL-1 receptor antagonist.
  - MOA: It inhibits the activity of IL-1 by binding to it and preventing cell signaling.
  - Therapeutic uses:
    - ✓ Adults with RA who have failed one or more nonbiologic DMARDs.
    - ✓ Recommended in specific situations in JIA.

- **Costimulation modulators: (Abatacept)**
  - MOA: Interferes with T-cell signaling, ultimately blocking T-cell activation and leading to **anergy (lack of response to an antigen)**
  - Route of administration: S.C. or IV.
  - Therapeutic uses:
    - ✓ Indicated as monotherapy.
    - ✓ In combination with nonbiologic DMARDs following inadequate response to methotrexate or anti-TNF agents.
    - ✓ For the treatment of moderate to severe JIA.

- **Anti-CD20 monoclonal antibody: (Rituximab)**
  - genetically engineered chimeric anti-CD20 monoclonal antibody
  - MOA: causes B-lymphocyte depletion in bone marrow and synovial tissue by activating apoptosis.
  - Therapeutic uses:
    - ✓ Rituximab is indicated for patients with moderate to severe RA and a history of inadequate response to one or more TNF antagonist therapies.
    - ✓ Contraindicated in pregnancy: should be discontinued 1 year prior to planned conception.

- Adverse effect:
  - ✓ Fatal infusion reactions, severe mucocutaneous reactions, hepatitis B reactivation, and progressive multifocal leukoencephalopathy.
  - ✓ It carries a black-box warning: when the drug has a significance side effects FDA puts it in a black-box warning list.
  - ✓ The benefits of rituximab must be tempered against the safety concerns reported with use of rituximab in the oncology setting, because it can causes a rare types of cancer like blood cancer and immune system cancers.

- Patients with RF-positive RA tend to respond more favorably to rituximab than patients with RF-negative disease. Explanation : patients with RA usually produce auto-antibodies called RF (rheumatoid factor) this case is called RF-positive RA but sometimes the patients serum doesn't contain these factors so the case is called RF-negative RA , even if the absence of them, the case is RA and the doctor depends on signs and symptoms to diagnose the disease.

• Interleukin-6 antagonists:

- Why do we use them? Because…
  - ✓ IL-6 production is increased in patients with RA.
  - ✓ High levels of IL-6 are indicative of joint damage and disease activity.
  - ✓ IL-6 plays a significant role in the pathogenesis of anemia associated with RA.
- Two types of IL-6 antagonists:

1. Tocilizumab:

- An anti–IL-6 receptor monoclonal antibody
- MOA: inhibits the binding of IL-6 to the IL-6 receptor.
- Route of administration: S.C. injection or IV infusion.
- Therapeutic uses:
  - ✓ Treatment of moderate to severe RA and JIA.

2. Sarilumab:

- is an IL-6 receptor antagonist
- MOA: binds to soluble and membrane-bound IL-6 receptors.
- Therapeutic uses:
  - ✓ It is indicated for treatment of moderate to severe RA following inadequate response or intolerance to one or more DMARDs.
  - ✓ It is not FDA approved for JIA.

❖Janus-kinase (JAK) inhibitors: (Tofacitinib)

- a synthetic small molecule rather than a large protein produced by recombinant DNA techniques
- MOA: selectively inhibits Janus kinases, with greatest affinity for JAK3.
- Janus-kinase is an enzyme that involved in intracellular cascade that occur after stimulation of JAK/STAT receptors (like cytokines receptors).
- Route of administration: orally (an advantage over biological DMARDs)
- Therapeutic uses:
  - ✓ treatment of moderate to severe RA as monotherapy.
  - ✓ Treatment of moderate to severe RA in combination with nonbiologic DMARDs.
  - ✓ Combination administration with biologic DMARDs is inappropriate due to increased immunosuppression and subsequent increased infection risk.

❖Selecting disease-modifying therapy:

- The decision to select a particular agent generally is based on
  - The prescriber's comfort level with monitoring medication safety and efficacy.
  - severity of disease activity
    - ✓ low activity use a monotherapy
    - ✓ high activity use a combination
  - The frequency and route of administration: the patient's comfort level or manual dexterity to self-administer subcutaneous injections.
  - the cost: especially biologic DMARDs
  - the availability of insurance coverage

❖RA drugs could affect fertility!

- Male patients with RA must receive counseling about the effects of certain medications on their fertility and potential harm to the fetus.
- Note from the previous lecture: Low-dose corticosteroids, certain NSAIDs, may be considered during pregnancy.