Medical Management of Rheumatoid Arthritis (RA)

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Educational objectives – ABC…

- Appreciate the epidemiology of RA
- Be able to diagnosis of RA
- Competent in managing RA with medically DMARDs and when to use them
- Educationally improved to score 100% in the final questions!
Some questions to set the scene:

- In your experience, which of the following is the most important barrier to the optimal management of rheumatoid arthritis? (select only one)
  - Delayed referral to a specialist
  - Lack of biomarkers to tailor treatment strategies
  - Side effects of medications

- How confident are you that you are up-to-date in the diagnosis and management of rheumatoid arthritis? (select only one)
  - Not at all confident
  - Confident
  - Very confident
What is Rheumatoid Arthritis

- RA is the most common inflammatory arthritis
- Affects 1% of the population
- Two to three times more common in women
- Can affects infants up to elderly persons
- Most commonly the onset is between 40s and 60s
- Cause is unknown
- Results in inflammation of the synovial tissue leading to tender and swollen joints which can lead to destruction and damage of joints
- High morbidity – 50% do not work after 10 year
- Higher mortality – approximating lymphoma and CVD
Diagnosis of RA

- **Clinical**
  - Symmetrical small joint inflammation
  - Early morning stiffness > 45 minutes
  - Family history
  - Reduced ability to perform activities of daily living

- **Lab results**
  - Raised ESR and CRP
  - Normochromic normocytic anaemia
  - Raised platelet count
  - Raised alkaline phosphatase
  - Positive rheumatoid factor – 10% don’t have RA and 25% are negative for RF
  - Positive anticyclic citrullinated peptide antibodies

- **X-ray changes**
  - Erosive changes
Medical management of RA

- Successful only if treated early (\(\leq 3\) years)
- Window of opportunity to achieve maximum benefit
  - 53\% respond if treated within 1 year of diagnosis
  - 43\% between 1 and 2 years
  - 35\% if > 10 years duration

- In rheumatoid arthritis (RA), which factor is most predictive of a successful response to treatment?
  - Number of affected joints
  - Duration of symptoms
  - Disease activity score
  - Radiographic progression
Case study - Initial visit

- A 35-year-old woman presents with:
  - morning stiffness of at least 45 minutes
  - pain and swelling of the joints in her hands and feet
  - fatigue for the first time in her life.

- As the mother of 2 children ages 5 and 7 years, she has found it difficult to keep up with the needs of her family. She reports difficulty with simple tasks such as opening bottles and helping her 5-year-old son button his shirt.

- Smokes about half a pack of cigarettes per day and drinks no more than 1 or 2 alcoholic beverages a week.
On physical examination and investigations

- Clinically and laboratory markers:
  - She had 13 tender and 12 swollen joints
  - Patient global assessment VAS = 6
  - Physician global assessment VAS = 6
  - ESR = 54
  - CRP = 3

- Which disease assessment tool is most useful to you in determining a change in therapy for this patient in your clinical practice?
  - HAQ
  - DAS28
  - ACR response
DAS28 and HAQ

- **DAS28**
  \[0.56\sqrt{\text{TJC28}} + 0.28\sqrt{\text{SJC28}} + 0.70\ln(\text{ESR}) + 0.014\times(\text{GH})\]

- **HAQ**
  - Difficulty in performing activities of daily living
    - 20 items (activities) over 8 categories and queries about use of help or aids
    - Higher score reflects greater disability
ACR response criteria:

- In RA – 68 tender and 66 swollen joints

- The other elements in the ACR scoring system:
  - VAS scores of patient pain
  - Patient global VAS
  - Physician global VAS
  - Health Assessment Questionnaire (HAQ)
  - CRP or ESR

- To achieve an ACR 20, 50, or 70 response, at least 20%, 50%, or 70%, respectively, improvement in tender and swollen joint counts and three of the above five scores
Investigations and management

- DAS28 at 6.7, which reflects high disease activity.
- HAQ score is 1.8, indicative of severe functional impairment.
- X-rays of her hands and feet are normal.

She was started on low-dose MTX, 7.5 mg/wk, plus folic acid, 1 mg/d, along with naproxen, 500 mg twice daily.

- Methotrexate is the established gold-standard treatment for active RA.
Another question!

Using a traditional approach to treatment, what are the goals of therapy for this patient?
- Control of clinical signs and symptoms
- Restoration of function
- Inhibition of radiographic progression
- Remission
Three months after the initial visit

- She reports no improvement.
- Her morning stiffness in the hands and feet still lasts at least 45 minutes, and her fatigue level is unchanged.
- Her tender and swollen joint counts remain unchanged at 13 tender and 12 swollen joints.
- The patient and physician global assessments also remain unchanged.
- ESR is 51 and calculated DAS remains unchanged at 6.7.
Crucial questions!!

How would you adjust her medication if she has active disease at 6 months, 9 months, 12 months?

- Optimize the dose of the MTX
- Switch to another DMARD
- Add a second DMARD
- Add a third DMARD
DMARDs

- Methotrexate
- Leflunomide
- Hydroxychloroquine
- Sulphasalazine
- Gold
Methotrexate

- Methotrexate is the most effective DMARD
  - it alleviates the signs and symptoms of RA
  - decreases the ESR
  - raises the Hb
  - slows the rate of bone erosion in RA

- Methotrexate is usually given in weekly oral doses, beginning at 10 mg and, if necessary, increasing to 25 to 30 mg weekly over the next 6 months
  - Subcutaneous administration increases bioavailability
- Over 70% of patients have a response to methotrexate, and half remain on the drug for at least 5 years.
  - patients' sense of well-being is often dramatically improved
  - Inflammation usually reappears within weeks after discontinuance
Monitoring of hematologic and liver parameters every 4 to 8 weeks is required
- Other adverse reactions to methotrexate include nausea, stomatitis, leukopenia, diarrhea, and elevations of serum aminotransferase levels
- Idiosyncratic interstitial lung disease can develop even at low doses
- Methotrexate is a potent teratogen and should not be used in women of childbearing age unless they are using a reliable form of contraception

Risk factors for toxicity include alcoholism, diabetes, obesity, advanced age, and renal disease. Some of these toxicities (especially oral ulcers) can be minimized by prophylactic administration of folic acid, 1 mg/day

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Leflunomide

- Leflunomide is an effective antirheumatic agent that blocks the pyrimidine synthesis required for stimulated B and T lymphocytes to proliferate
  - Randomized, controlled trials have demonstrated that leflunomide is as effective as methotrexate in the treatment of active RA
  - In addition to being clinically effective, leflunomide slows radiographic progression of RA

- Because the half-life of leflunomide is 2 weeks, loading doses of 100 mg/day for 3 days are necessary to achieve therapeutic blood levels promptly, followed by daily dosing with 20 mg/day.
Leflunomide can be used in combination with methotrexate, at a lower dose of 10mg/day and these patients must be followed very carefully for hepatotoxicity.

Adverse effects include diarrhoea, liver toxicity, rash, oral ulcers, and reversible hair loss.

It is a potent teratogen and should not be used in women of childbearing age unless they are using a reliable form of contraception.
Antimalarial Drugs and Sulfasalazine as Single and Combination Agents

- Hydroxychloroquine response rate is lower than MTX but it is relatively safe so is ideal for patients with mild early disease.
- Adverse reactions include GI problems, skin rashes but most importantly but rarely irreversible retinopathy and this can be minimized with regular eye checks.

- Sulfasalazine is effective in at least 30% of patients at a dosage of 2 to 3 g/day in divided doses.
- Only moderate side effects have been reported, especially GI upset and thus it is well tolerated; over 30% of patients continue to take it for at least 5 years.

- A significant percentage of RA patients do not experience satisfactory symptomatic relief with a single DMARD, thus combination therapy have been advocated.
Gold Salts

- Injectable gold (myocrisin) decreases inflammation and increase the likelihood of remission.
- Treatment usually consists of intramuscular test dose of 10 mg, followed by 50 mg once weekly for 20 weeks, then fortnightly and monthly if the response is satisfactory at this point.
- The response rate to gold is about 30%, although toxicity and lack of efficacy result in discontinuance in almost 90% of patients within 5 years.
- Major adverse side effects involve hematologic, renal, and dermatologic reactions.
- Oral gold preparations appear to be less toxic than injectable ones but are less effective.
Other drugs used in RA

- NSAIDs
- Steroids
- Biologics
- Other immunosuppressive drugs
  - Cyclosporin
  - Cyclophosphamide
  - Azathioprine
Pharmacotherapy - NSAIDs

- Inhibits Cox enzyme which catalyses the production of prostaglandins
- Cox-1 is constitutive enzyme – PGs serve physiological functions
- Cox-2 is inducible enzyme – PGs are pro-inflammatory
- Use of Cox-2 in high risk patients
  > 65 years, smoking, prior ulcer disease, steroid use
Side effects of NSAIDs

- Gastrointestinal
  - Dyspepsi, ulcers, bleeding, perforation, stomatitis
- Renal
  - Oedema, increase creatinine, renal failure, interstitial nephritis, papillary necrosis
- Cardiac
  - Fluid retention, cardiac failure, hypertension
- Neurological
  - Headache, dizziness, nausea
- Pulmonary
  - Exacerbation of asthma
- Dermatological
  - Erythema multiforme, bullous, urticaria, fixed drug eruption
- Haematological
  - Aplastic anaemia, haemolytic anaemia
- Hepatitis
- Systemic
  - Anaphylaxis

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Corticosteroids

- Intra-articular, intra-synovial
- Oral
- Parenteral
Biologic therapy

- Tumour necrosis factor (TNF) antagonists
- Interleukin-1 antagonists
- B cell depletion
- T cell co-stimulator modulation
Cytokines in Inflammations

Pro-inflammatory

TNFα

IL-1

Anti-inflammatory

IL-1Ra

IL-10

sTNFR
Tumour necrosis factor (TNF) antagonists
Etanercept, Infliximab, Adalimumab

- **Etanercept** (25 mg sc twice a week)
  - Soluble TNF receptor which binds to TNF-alpha and beta
  - Licensed for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, juvenile chronic arthritis

- **Infliximab** (intravenous 3-5 mg/kg at week 0, 2, 6, every 8 weeks)
  - Chimeric monoclonal anti-TNF antibody which neutralises soluble and membrane bound TNF-alpha. Down-regulates adhesion molecules and inhibits angiogenesis
  - Licensed for rheumatoid arthritis and Crohn’s disease

- **Adalimumab** (40 mg sc every other week)
  - Fully humanised monoclonal anti-TNF antibody
  - Licensed for rheumatoid arthritis
TNF antagonists

- **Chimeric mouse-human antibody** against soluble and membrane TNF
- **Soluble TNF receptor** – binds to TNF-α and β
- **Human antibody**
- **Others are in development**
Other biologic therapy

- **Interleukin-1 antagonists**
  - **Anakinra** (100 mg sc daily)
  - IL-1 receptor antagonist
  - Licensed for treatment of RA

- **B cell depletion**
  - **Rituximab** (2 1000mg iv two weeks apart, may be repeated every 6-9 months)
  - Chimeric anti-CD20 antibody
  - Licensed for treatment of B cell lymphoma
  - Shown to be effective in controlling disease in RA and SLE patients

- **T cell co-stimulator modulator**
  - **Abatacept** (iv 10mg/kg, at day 0, 2, 4 and every 4 weeks)
  - Fully human soluble fusion protein produced by recombinant DNA with inhibitory activity on T lymphocytes
  - Licensed for treatment of rheumatoid arthritis
Algorithm for treatment of RA

Diagnosed RA
Start NSAIDs and MTX

Education Specialist nurses
Physiotherapy, OT, chiropody
Psychology, dietician, SW

Single agents
Leflunomide
SZP, OHCQ, Gold

Combination
Therapy with or without biologics

-suppressives

Steroids

Surgical

Immuno-
Your local rheumatologist starts a 35 year old woman with rheumatoid arthritis on infliximab. The patient returns to you a week after starting the drug. The rheumatologist told her something about the new treatment but she has more questions. She wants to know how it works. How does infliximab work?

- It blocks dihydrofolate reductase
- It inhibits the activity of tumour necrosis factor
- It interferes with pyrimidine synthesis
- It inhibits thymidylate synthase
Question 2

A 30 year old woman with rheumatoid arthritis has taken several drugs for her disease. Which of the following has the fastest onset of action?

- Methotrexate
- Sulphasalazine
- Etanercept
- Azathioprine
Question 3

A 30 year old woman is diagnosed with rheumatoid arthritis. She has had to take a lot of time off work and wonders what her long-term outlook is. What percentage of patients with rheumatoid arthritis are unable to work 10 years after its onset?

- 35%
- 50%
- 65%
- 80%
Question 4

A 35 year old woman who has had rheumatoid arthritis for six years starts taking infliximab. After three months of treatment she has had no response. What is the best course of action?

- She should stop the drug
- She should continue it for another month
- She should continue it for another three months
- She should continue it for another six months
A 40 year old woman complains of painful and swollen joints in both hands for the past two months. She also complains of feeling stiff in the mornings. On examination there are signs of arthritis affecting her wrists, metacarpophalangeal joints, and elbows. Rheumatoid factor and antinuclear antibodies are present. What is the most likely diagnosis?

- Mixed connective tissue disease
- Polymyalgia rheumatica
- Rheumatoid arthritis
- Scleroderma
- Systemic lupus erythematosus
Question 6

A 30 year old woman complains of pains and stiffness in her joints. You suspect rheumatoid arthritis clinically, but are surprised that her test for rheumatoid factor is negative. What percentage of patients with rheumatoid arthritis have a negative rheumatoid factor test?

- 10%
- 25%
- 40%
- 55%
Question 7

A 30 year old man complains of pains in his legs. He also says he has oral and genital ulcers. On examination you find evidence of arthritis affecting his ankles and knees and also uveitis. His rheumatoid factor test is negative. What is the most likely diagnosis?

- Reactive arthritis
- Seronegative rheumatoid arthritis
- Gonococcal arthritis
- Behcet's syndrome
- Viral arthritis