Pharmacotherapy 2

Rheumatoid Arthritis

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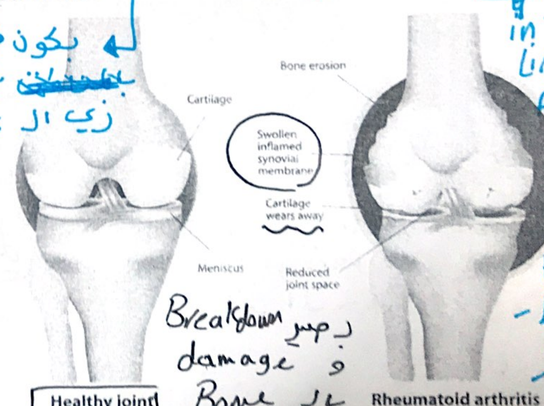
Rheumatoid Arthritis (RA)

General Principles

- ✓ RA is a systemic disease of unknown etiology that is characterized by a symmetric inflammatory polyarthritis, extra-articular manifestations (rheumatoid nodules, pulmonary fibrosis, serositis, scleritis, vasculitis), and serum RF in up to 80% of patients.
- ✓ The course of RA is variable but tends to be chronic and progressive.



Diagnosis

✓ Clinical Presentation: عادة بيلش بال small joints تحت الايدين

- Insidious onset of pain, swelling, and morning stiffness in the hands and/ or wrists or feet. ناس عاجرين ل مفاصله لما يتحرك الصبح ممكن ال stiffness لحتى اكثر من نص ساعة
- Synovitis may be evident on examination of the metacarpo-phalangeal, proximal interphalangeal, wrist, or other joints.
- Rheumatoid nodules may be palpated most commonly on extensor surfaces. → لما يكون المفصل مو مثني
- Suspect the diagnosis in patients presenting with symmetric arthritis in three or more joints especially involving small joints and associated with morning stiffness lasting more than 30 minutes.

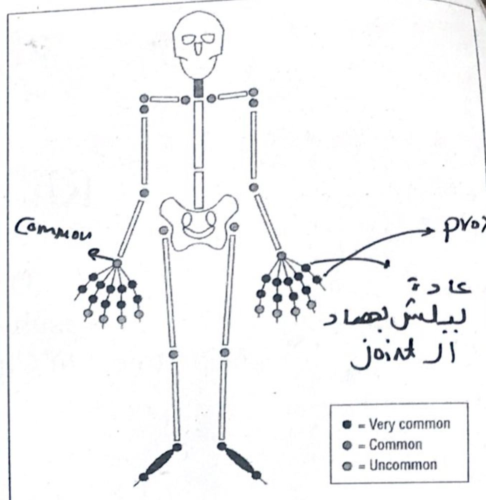


FIGURE 107-2 Patterns of joint involvement in rheumatoid arthritis.

① في scoring system بعتمد على number of joints affected ① و ال size of joints ② , duration of symptoms ③

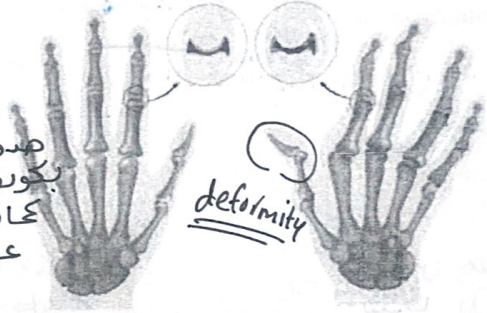
④ ESR - RF

ازا 6/10 ← بيتشخص المريض RA

② في scoring تانية لل disease activity او اي هيه severity of disease

✓ Diagnostic Testing:

- RF may be positive in 80% of patients. Cyclic citrullinated peptide (CCP) antibodies may be detected in 50%– 60% of patients with early RA.
- Hand and wrist radiographs may show early changes of erosions or periarticular osteopenia.
- Musculoskeletal MRI and ultrasonography may be used to demonstrate clinically inapparent synovitis or erosions.



Normal Rheumatoid Arthritis

* ESR
* C reative protien

joint displacement زي

Treatment

- ✓ Most patients can benefit from an early aggressive treatment program that combines medical, rehabilitative, and surgical services designed with three distinct goals:
  - early suppression of inflammation in the joints and other tissues → يبي اقلل الـ swelling و الـ pain
  - maintenance of joint and muscle function and prevention of deformities
  - repair of joint damage to relieve pain or improve function.

physical mental therapy

- ✓ DMARDs appear to alter the natural history of RA by retarding the progression of bony erosions and cartilage loss. They do not reverse joint damage that has already occurred. ← ازا تشخص RA خلص not reversible بس يحافظ عليه ما يزيد
- ✓ Because RA may lead to substantial long-term disability (and is associated with increased mortality), the standard of care is to initiate therapy with such agents early in the course of RA.
- ✓ Once a clinical response has been achieved, the chosen drug usually is continued indefinitely at the lowest effective dosage to prevent relapse.

Methotrexate
Sulfasalizen
Leflunomide
Hydroxychloroquine
azathioprine
Cyclosporine

← [1] conventional DMARDs
[2] Tumor nicrosis Biologics
[3] Non-Tumor nicrosis Biologics
[4] agent في رابع

- ✓ An established diagnosis of RA along with any evidence of disease activity is an indication to initiate disease-modifying therapy. مجرد ما شخصنا خلص بدنا نبلش بال DMARDs
- ✓ Initial monotherapy with NSAIDs or steroids is no longer considered appropriate under usual circumstances. يعني هون بحكي Monotherapy ← فابعبر راح يوصل الـ DMARDs لاعطيه منصم عادي بعبر
- ✓ Methotrexate typically is the initial choice for moderate-severe RA. Leflunomide is an alternative.
- ✓ Hydroxychloroquine or sulfasalazine can be used as the initial choice in very mild RA. بحالة preg او بدها تصير preg
- ✓ If response to the initial agent is unsatisfactory after an adequate trial (or if limiting toxicity supervenes), other DMARDs or a biologic agent can be added or substituted.

بعطي NSAIDs او steroids لحد ما الـ DMARDs يبلش مفعوله

Tumer Nicrosis Factor Agents inhin

non - Tumer nicrosis

prednison = will work as anti-inflammatory وتأثيره بكون سريع

Conventional demardes ممكن اعطي من ال ٢-٣ مع بعض بس ما بعطي 2 biologic سوا

* Choice of pharmacology agents?
1. disease activity (Level of disease activity) Low - Moderate - severe
2. Comorbidites pt have.
3. Previous Trail - Medication شو اخد من قبل ادوية
4. pt prefrance

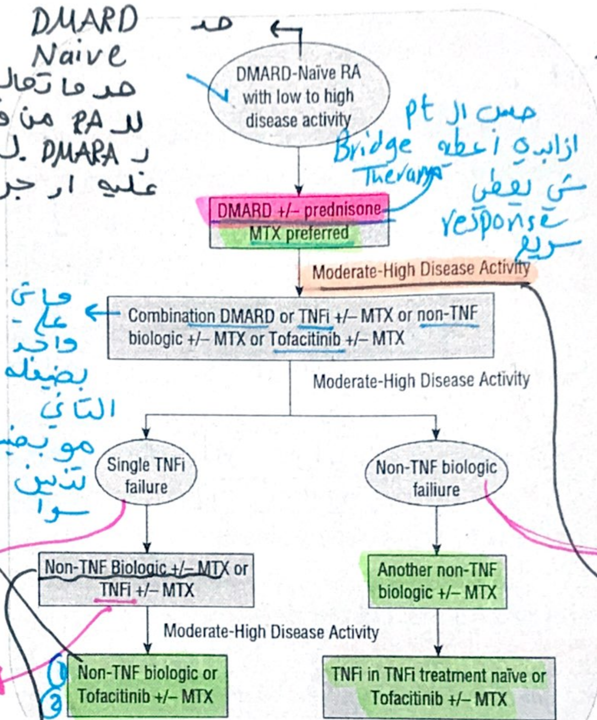


Figure. Treatment algorithm for rheumatoid arthritis based on the American College of Rheumatology guidelines. (DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; TNF, tumor necrosis factor.)

Moderate-High disease activity →
1. DMARDs
2. TNFi → infliximab ± MTX → add on
3. non-TNFi ± MTX
4. Tofacitinib ± MTX

Conventional DMARD + Biological (TNFi)

Tofacitinib → Synthatic agent

A. Conventional DMARDs

DMARDs → TNFi → Non-TNF

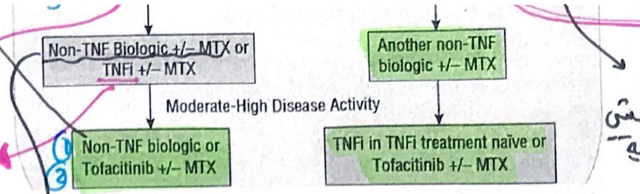
Methotrexate:

- ✓ It is a purine inhibitor and folic acid antagonist. RA is its most common indication.

  IM, SC, oraly

- ✓ Dosage and administration: Typically, methotrexate is administered as a single PO dose once a week starting with 7.5– 10 mg. Clinical response is usually noted in 4-8 weeks.

TNF, tumor necrosis factor.)



Moderate –High disease activity →
1 DMARDs
2 TNFI → inflixmab
MTX لحاله او مع → add on
3 non- TNFi ± MTX
4 Tofacitinib ± MTX

Conventional DMARD + Biological (TNFI)

Tofacitinib → synthatic agent

A. Conventional DMARDs

لانه عادة صيل يتكون الخطوات
DMARDs → TNFi → Non-TNF

Methotrexate:

- ✓ It is a purine inhibitor and folic acid antagonist. RA is its most common indication.
  IM , SC , oraly
- ✓ Dosage and administration: Typically, methotrexate is administered as a single PO dose once a week starting with 7.5– 10 mg. Clinical response is usually noted in 4-8 weeks.
- ✓ The dosage can be increased by 2.5- to 5-mg increments every 2– 4 weeks to a maximum of 25 mg/ wk or until improvement is observed.
- ✓ Dosages above 20 mg/ wk are generally given by SC injection to promote absorption.
- ✓ Contraindications and side effects:
  - Methotrexate is teratogenic and should not be used during pregnancy.
  - It should also be avoided in patients with significant hepatic or renal impairment.
  - Folic acid at a dosage of 1-2 mg daily may reduce toxicity without attenuating efficacy.
  - Concomitant use of TMP-SMX should be avoided.
  - Serologic testing for hepatitis B and C should be included before initiation of therapy.

X preg X TMP– SMX
X hepatic , renal

- Minor side effects include GI intolerance, stomatitis, rash, headache, and alopecia.
- Bone marrow suppression may occur, particularly at higher doses.
- Blood and platelet counts should be obtained before initiation, every 4 weeks during the first 3-4 months or if the dose is changed, and every 8 weeks thereafter.
- Macrocytosis may precede serious hematologic toxicity and is an indication for folate supplementation, dose reduction, or both.
- AST, ALT and serum albumin should be obtained initially at 4- to 8-week intervals during the first 3-4 months of therapy or if the dose is changed.
- Patients on a stable dose should be monitored every 8-12 weeks after 3 months of therapy and every 12 weeks after 6 months of therapy.
- Alcohol consumption increases the risk of methotrexate hepatotoxicity.
- Hypersensitivity pneumonitis may occur but usually is reversible.
- Rheumatoid nodules may develop or worsen, paradoxically, in some patients on methotrexate.

Sulfasalazine:

- ✓ It is useful for treating synovitis in the setting of RA.
- ✓ Dosage: Initial dosage is 500 mg PO daily, with increases in 500-mg increments weekly until a total daily dose of 2000– 3000 mg (given in evenly divided doses) is reached.
- ✓ Clinical response usually occurs in 6– 10 weeks.
- ✓ Contraindications and side effects:
  - Sulfasalazine should be used with extreme caution in patients with G6PDD.
  - Sulfasalazine should not be used in patients with sulfa allergy.
  - Nausea is the principal adverse effect, can be minimized by enteric-coated preparation.
  - Periodic monitoring of blood and platelet counts is recommended.

Clinical response 4-8 weeks ← (2-4 weeks) الجرعة كل MTX بنزيد ال

Clinical response (6-10) weeks ← weekly الجرعة كل Sulfasalizim بنزيد ال

Hydroxychloroquine: ✓ preg

- ✓ It is an antimalarial agent that is used to treat dermatitis, alopecia, and synovitis in SLE and mild synovitis in RA.
- ✓ Dosage: Hydroxychloroquine typically is given at a dosage of 4– 6 mg/ kg PO daily (200-400 mg) after meals to minimize dyspepsia and nausea.
- ✓ Contraindications and side effects:
  - Hydroxychloroquine should be used with caution in patients with porphyria, G6PDD, or significant hepatic or renal impairment.
  - It is safe during pregnancy.
  - The most common side effects are allergic skin eruptions and nausea. Serious ocular toxicity (corneal deposits and retinopathy) occurs, but it is rare with currently recommended dosages. Ophthalmologic evaluation should be performed on an annual basis.

RAPE

HX9 → ↓ nausea → Take with or after Meal

Sulfa salizin → ↓ nausea → Enteric - Coated preperation

Leflunomide:

- ✓ It is a pyrimidine inhibitor that has been approved for the treatment of RA.
- ✓ Dosage and administration: Treatment is begun with 10 or 20 mg PO daily.
- ✓ Clinical response is generally seen within 4– 8 weeks.
- ✓ Contraindications and side effects:
  - Leflunomide is teratogenic and has a very long half-life:
    - Women who plan to become pregnant must discontinue the drug and complete a course of elimination therapy with cholestyramine, 8 g PO tid for 11 days.
    - Plasma levels should then be verified to be < 0.02 mg/ L on two separate tests at least 14 days apart before pregnancy is considered.
  - Leflunomide is contraindicated in patients with significant hepatic dysfunction or in those who are receiving rifampin.

Leflonamide X Rifumpin Hepatic dys

Wash out with cholestyramine 8g - po - لمدة ١١ يوم → Leflonomide

Rifampin → enzyme inducer → يزيد ال Metabolism → يزيد risk of toxicity of leflunamide

- GI side effects are the most common:
  - Diarrhea occurs in up to 20% of patients and may require discontinuation of the drug.
  - Dosage reduction to 10 mg/ d may provide relief while maintaining efficacy.
  - Loperamide can be used for symptomatic relief.
- Elevations in serum transaminase levels may occur and should be measured at baseline and then monitored periodically.
- The dosage should be reduced for confirmed twofold elevations, and greater elevations should be treated with cholestyramine and discontinuation of leflunomide.
- Rash and alopecia may occur during therapy.

↳ Hydroxi حكينا ال

ازا كان ال Trasminase مرتفع Two folds → بنقلل الجرعة

Leflunomide → serum Transaminase (Lab Monitoring)

ازا الكرّون عن Two fold ال Base line بدنا نعمل Wash out
↳ cholestyramine
Leflunomide ونوقف ال

* Hydroxichloroquin → يعالج alopecia ال
* Leflunomide → يسبب alopecia

B. Anticytokine Therapies (Biologic DMARDs): ⇄ TNFi / Non – TNFi

1) TNF Inhibitors

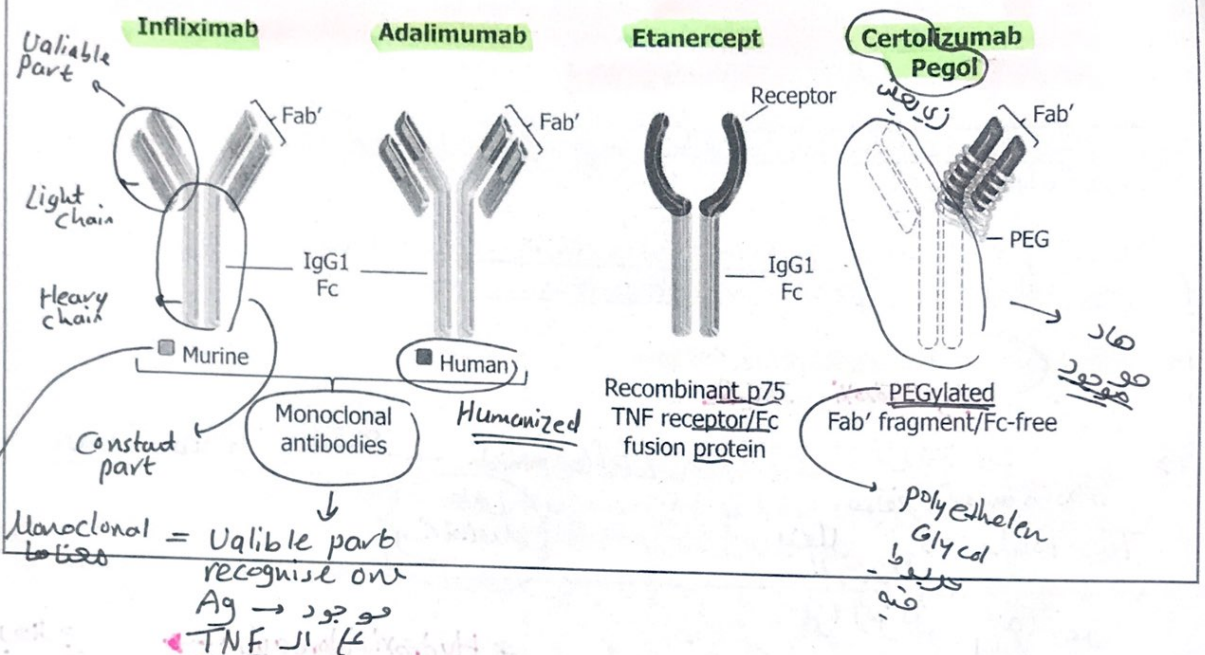
B. Anticytokine Therapies (Biologic DMARDs): TNFi / Non – TNFi

1) TNF Inhibitors

- ✓ They have been approved for treatment of RA.
- ✓ These agents are used in patients with moderate to severe RA who have failed a trial of one or more DMARDs.
- ✓ The effect of these agents on synovitis can be dramatic, with responsive patients sometimes reporting the onset of symptomatic benefits within 1– 2 weeks.
- ✓ In addition to their symptomatic benefits, these agents appear to retard joint damage significantly.
- ✓ They include etanercept, infliximab, adalimumab, golimumab, and certolizumab.

They delay disease activity وما بيتبعها من joint damage

TNF Inhibitors:



Monoclonal = Ualible part recognise one Ag → موجود على الـ TNF

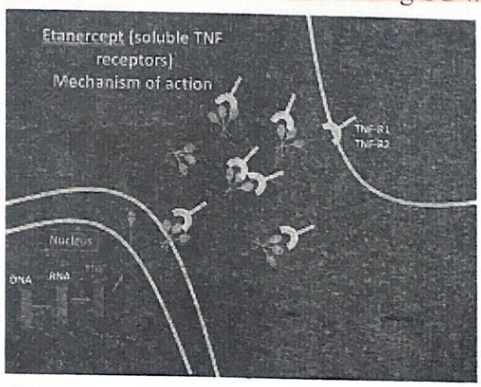
Surface الـ several Ag polyclonal

Mouse Moice = فار

✓ Etanercept:

- It is a fusion protein that consists of the ligand-binding portion of the human TNF receptor linked to the Fc portion of human IgG. It binds to TNF, blocking its interaction with cell surface receptors, thus inhibiting the inflammatory and immunoregulatory properties of TNF.

- It is given in a dosage of 25 mg SC twice a week or 50 mg SC weekly.

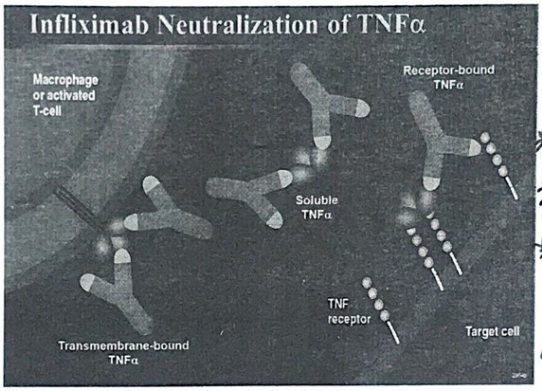


25 → Twice
50 → once

✓ **Infliximab:**

- It is a chimeric monoclonal antibody that binds specifically to human TNF-α, blocking its proinflammatory and immunomodulatory effects.
- IV infusion in conjunction with methotrexate (reduce production of neutralizing antibodies against infliximab).
- Infliximab infusions of 3 mg/ kg at initiation, at 0, 2 and 6 weeks, and every 8 weeks thereafter, along with methotrexate at a dose of at least 7.5 mg/ wk.

ممكن يصير من الجسم response ضد هاد الي جاي من بره لازم Neutrilizes AB from body



Infliximab
↓
* + MTX → 7.5 mg/wk
* SC
* intial = 3mg/kg

بعدين بعد 2weeks بعيد الجرعة و بعدين كل أسابيع من الجرعة الاولى لـ بعض بعد ٤ اسابيع من الثانيه) باخذ الجرعة الثالثة بعدين كل ٨ اسابيع يعني كل شهرين

✓ **Adalimumab:** prefilled syringe / SC injection

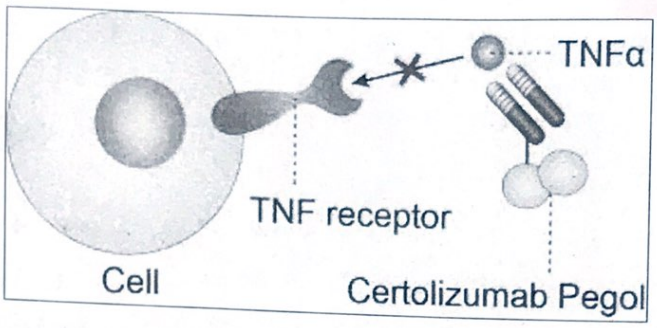
- It binds to TNF- α & blocks its interaction with the p55 and p75 cell surface TNF receptors.
- It is available as a prefilled syringe or pen for SC injection.
- Typical dosing for RA is 40 mg every 2 weeks when used with methotrexate. The dose can be increased to 40 mg weekly if it is not being used with methotrexate.

✓ **Golimumab:** monthly or infusion every 8 weeks. Methotrex ممكن مع او بدون

- It is a human monoclonal antibody that binds to human TNF-α.
- It can be given as a monthly injection or an infusion every 8 wks after an initial loading dose.

✓ **Certolizumab pegol:** Monthely

- It is a pegylated humanized Fab fragment of an anti-TNF-α monoclonal antibody.
- It is given monthly after an initial loading dose.



✓ Contraindications and side effects of TNF inhibitors:

- These drugs are contraindicated in patients with acute or chronic infections, and if serious infection or sepsis occurs, the drug should be stopped. Hepatitis, TNC
- Those with a history of recurrent infections and those with underlying conditions that may predispose to infection should be treated with caution and counseled to be vigilant for signs and symptoms of infection.
- Upper respiratory and sinus infections are most common. TB has also been noted, and a tuberculin skin test and CXR should be obtained before beginning therapy.
- These agents are also contraindicated in patients with CHF (usually with a LVEF < 30%).
- Patients undergoing elective surgery should discuss with their rheumatologist regarding the optimum duration to hold medications peri-operatively, this may depend upon the half life of the drug and post operative wound healing.

بعض ال agents زي infliximab ممكن نحتاج نعطي
Corticosteroid , APAP , antiHistamine بـ preTreatment

- Local injection site reactions are common with SC administration, particularly during the first month of therapy.
- Reactions are generally self-limited and do not require discontinuation of therapy.
- Serious systemic allergic reactions are rare but may occur with infliximab infusions. =N infusion
- A demyelinating disorder has been described as well as exacerbations of preexisting multiple sclerosis.
- The risk of nonmelanoma skin cancer is increased in patients who receive TNF blockers.
- It is unclear whether the frequency of occurrence of lymphoma is increased in patients who receive these agents. A black box warning, however, has been placed on the package insert of these agents.

part 2 21:00

لحد هلا فاني شي واضح انه ممكن يعملوا lymphoma بس شغلة ممكن نحكيها للمريض عشان يكون بالصورة

2) Non-TNF Inhibitors:

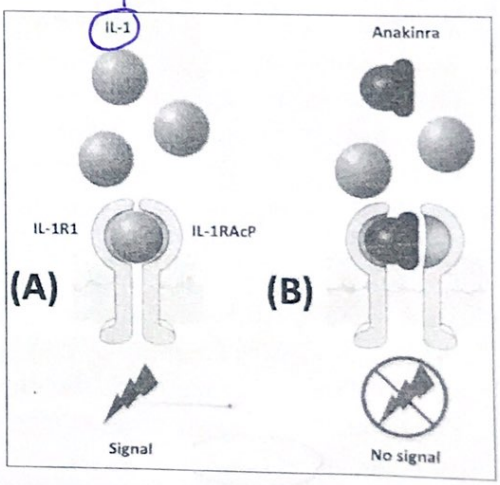
هوه واحد من ال Cytokines اللي الـ inflammatory و immunomodulatory بال RA effect

① Interleukin Inhibitors:

Signal ← للـ inflam بربط بال receptor تبعه و بصير عنا
No signal بصير IL-1 بربط بال receptor تبعه ال Anakinra بيجي هوه بربط

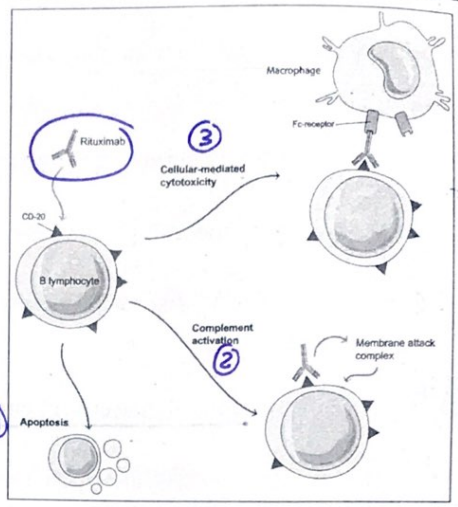
✓ **Anakinra:**

- It is a recombinant IL-1 receptor antagonist that is approved for use in RA.
- It blocks binding of IL-1 to its receptor, thus inhibiting IL-1 proinflammatory and immunomodulatory actions.
- It is given in a dosage of 100 mg SC daily.
- Similar to TNF blockers, it should not be prescribed to patients with ongoing or recurrent infections.
- Adverse effects include an increased frequency of bacterial infections and injection site reactions.



② B-Cell-Directed Therapy:

✓ Rituximab:



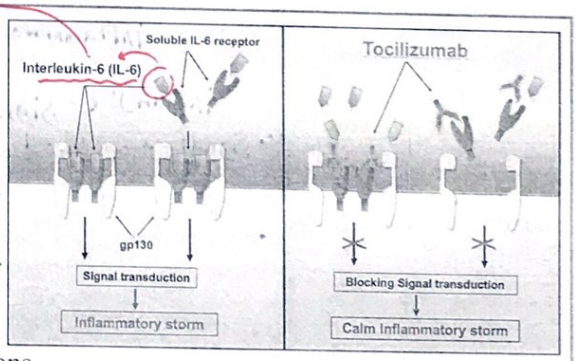
- It is a monoclonal antibody directed against CD20, a cell surface receptor found on B cells.
- CD20-positive B cells in peripheral blood are rapidly depleted after two infusions of 1 g rituximab 2 wks apart.
- Methotrexate is generally used as background therapy.
- The infusion can be repeated in 6- to 12-month intervals, based on patient symptoms.
- Infusion reactions are more common with the first dose and rarely fatal.
- Antihistamines, IV steroids, and acetaminophen are routinely given prior to infusion.
- SEs: Upper RIs, nasopharyngitis, UTI, serious infections, bronchitis, infusion reactions, bowel obstruction/perforation, blood cell disorders, and CV events.
- A CBC with differential should be obtained before treatment, with each infusion, & every 2-4 months.

* يعني مدة العلاج اسبوعين
جرعة اليوم وبعد اسبوعين كمان
وحده و بعدين ممكن نكرر
العلاج بعد (6-12) شهر

* عنا ال B lymphocy عليها CD-20
ال Rituximab (Monoclonal AB)
لما يرتبط بال CD-20 فيها
بيدخل ال cell بـ 3different pathways

* يرتبط بال receptor بتجه الي يكون اما soluble
ال Membrane bound فلما يرتبط بال recp
بصير Signal Trasduction ← inflammatory storm

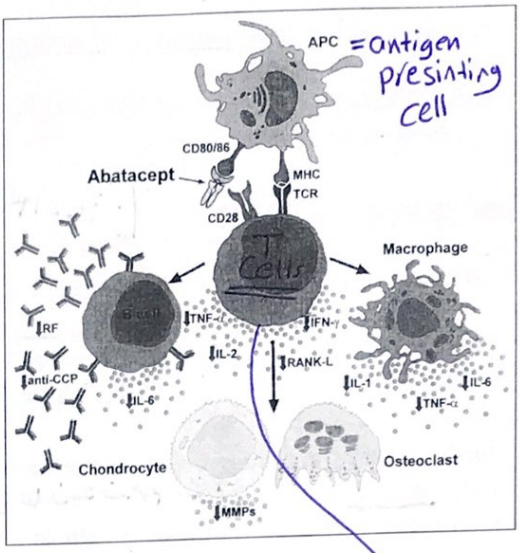
Tocilizumab:



- ✓ It is an antagonist of soluble and membrane-bound IL-6 receptors.
- ✓ It is given as an IV infusion or as an SC injection at a dose of 162 mg either weekly or every other week depending on the patient's weight (100 kg).
- ✓ The most common SEs: upper RIs, nasopharyngitis, headache, hypertension, increased liver enzymes, and injection site reactions.
- ✓ Tocilizumab can also cause GI perforation, neutropenia, thrombocytopenia, serious infections and malignancy.
- ✓ Baseline monitoring: neutrophils, platelets, lipid panel, AST, and ALT.
- ✓ Neutrophils, platelets, and liver enzymes should also be monitored 4 to 8 weeks after starting therapy and every 3 months thereafter. A lipid panel should be repeated after 4 to 8 weeks of treatment and every 6 months during treatment.
- ✓ Tocilizumab has the potential to increase the metabolism of drugs that are CYP450 substrates, particularly CYP3A4.

Abatacept:

- ✓ It blocks selective co-stimulation of T cells (inhibits T-cell activation by binding to CD80 & CD86).
- ✓ It is given as an IV infusion of 500-1000 mg every 4 weeks. كل شهر
- ✓ It is also available as an SC formulation that can be given 125 mg SC weekly with or without an initial loading dose.
- ✓ It is approved in patients with an inadequate response to biologic or nonbiologic DMARDs.
- ✓ Infections occur slightly more often than in placebo-treated patients.
- ✓ COPD exacerbations and respiratory infections are more common in patients with moderate to severe obstructive lung disease when treated with abatacept.



abatacept * بيجي يرتبط بال CD86/80 الموجودين على APC بمنع يصير activation لل Tcells بالتالي يقلل من cell activation ↳ ↓RF, Anti CCP

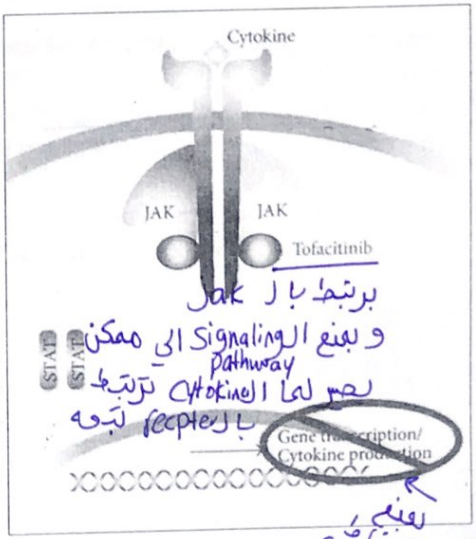
activation عشان يصيرلها T-cells ال
لازم يصير Co-stimulation من ال APC
CD86 / CD80 هنا antigen الي عليها
وال TCR المعزومين يرتبط بال CD86/80 الموجودين
على ال APC و يصيرلها (activation)

C. Target-Specific DMARDs

Synthatic not Biologic

Tofacitinib:

- ✓ It is an oral agent that inhibits Janus kinases or JAK that are needed for intracellular signaling in immune and hematopoietic cells.
- ✓ Tofacitinib can be used orally as 5 mg bid or an extended release tablet at 11 mg daily.
- ✓ Tofacitinib can be used as monotherapy or in combination with a synthetic DMARD as MTX.
- ✓ Common side effects are cytopenia and hepatic enzyme elevation.
- ✓ There is an increased risk of shingles.
- ✓ Lipid panel should be checked before and after start of therapy.



برتبط بال Jak
و بمنع الSignaling الي ممكن pathway
يصير لها الCytokine ترتبط
بالreceptors تبعه
يمنع ارتباط Cytokine

D. Other DMARDs

- ✓ Therapies such as azathioprine, cyclosporine, minocycline, and gold salts were previously used to treat RA.
- ✓ With the development of other DMARDs and biologics, they are now used infrequently and have no recent data to support their use.

Combinations of DMARDs

[يفضل ممكن اعشي المريض على Triple Therapy على ٣ ادوية]

- ✓ Combinations of DMARDs can be used if the patient has a partial response to the initial agent.
- ✓ Common combinations include methotrexate with hydroxychloroquine, sulfasalazine, or both.
- ✓ Methotrexate is commonly combined with TNF antagonists because there is evidence for additive efficacy and for a decrease in the formation of human antichimeric antibodies against the TNF blocker.
- ✓ Methotrexate and leflunomide may have additive hepatotoxicity, and this combination should be used cautiously. بنفضل ما نستخدم سوا
- ✓ Combination therapy with two biologic agents is contraindicated because of increased infectious complications.

2 biologic سوا ← لا

E. NSAIDs or selective COX-2 inhibitors

- ✓ They may be used as an effective adjunct to DMARD therapy & can provide symptomatic relief of pain and stiffness يتخدوا مع
- ✓ They do not slow disease progression and should not be used as monotherapy. ال DMARDs بس
- ✓ They have a more rapid onset of action than DMARDs and may be beneficial to "bridge" patients while DMARDs take effect.
- ✓ They have been found to increase the risk of serious CV thrombotic events, including MI & stroke.
- ✓ Their use is also associated with serious GI bleeding and ulcerations.

F. Glucocorticoids

كلهم ال non-selc / selective
بس بعدول اكتر

- ✓ They are not curative but may delay the formation of erosions with other DMARDs and are among the most potent anti-inflammatory drugs available.
- ✓ Indications for glucocorticoids include:
  1. symptomatic relief while waiting for a response to a slow-acting immunosuppressive or immunomodulatory agent
  2. persistent synovitis despite adequate trials of DMARDs and NSAIDs

(3) • severe constitutional symptoms (e.g., fever and weight loss) or extra-articular disease (vasculitis, episcleritis, or pleurisy).

✓ Oral administration of prednisone 5-20 mg daily usually is sufficient for the treatment of synovitis, whereas severe constitutional symptoms or extra-articular disease may require up to 1 mg/ kg PO daily.

✓ Although alternate-day glucocorticoid therapy reduces the incidence of undesirable side effects, some patients do not tolerate the increase in symptoms that may occur on the off day.

✓ Intra-articular administration may provide temporary symptomatic relief when only a few joints are inflamed.

✓ The beneficial effects of intra-articular steroids may persist for days to months and may delay or negate the need for systemic glucocorticoid therapy.

يوم اه يوم لا

لغي احنا خايفين من ال systemic بس ال undesirable effect هو بنعمل؟

① alternate-day = Treatment ممكن ندخلي

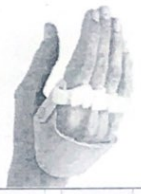
② few joints affected لو كان = Intra-articuler

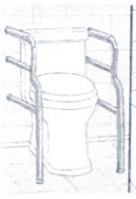
Nonpharmacologic Therapies

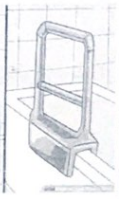
✓ Nonpharmacologic approaches for the treatment of RA include referrals to occupational and physical therapy, mental health, social work, reviewing pain coping skills, and providing patient education.

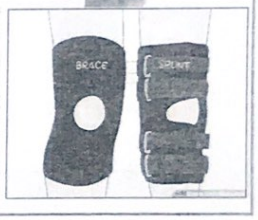
✓ Physical and occupational therapy can be effective and provide several benefits to improve pain and function such as exercises, appropriate footwear, splinting, adaptive equipment, assistive devices, orthoses as braces, and mobility aids.

✓ Weight loss can help decrease the stress on joints.









D. Other DMARDs

- ✓ Therapies such as azathioprine, cyclosporine, minocycline, and gold salts were previously used to treat RA.
- ✓ With the development of other DMARDs and biologics, they are now used infrequently and have no recent data to support their use.

Combinations of DMARDs

- ✓ Combinations of DMARDs can be used if the patient has a partial response to the initial agent.
- ✓ Common combinations include methotrexate with hydroxychloroquine, sulfasalazine, or both.
- ✓ Methotrexate is commonly combined with TNF antagonists because there is evidence for additive efficacy and for a decrease in the formation of human antichimeric antibodies against the TNF blocker.
- ✓ Methotrexate and leflunomide may have additive hepatotoxicity, and this combination should be used cautiously.
- ✓ Combination therapy with two biologic agents is contraindicated because of increased infectious complications.

E. NSAIDs or selective COX-2 inhibitors

- ✓ They may be used as an effective adjunct to DMARD therapy & can provide symptomatic relief of pain and stiffness
- ✓ They do not slow disease progression and should not be used as monotherapy.
- ✓ They have a more rapid onset of action than DMARDs and may be beneficial to "bridge" patients while DMARDs take effect.
- ✓ They have been found to increase the risk of serious CV thrombotid events, including MI & stroke.
- ✓ Their use is also associated with serious GI bleeding and ulcerations.

F. Glucocorticoids

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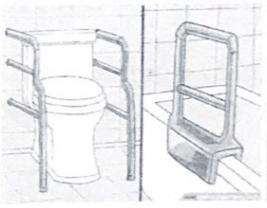

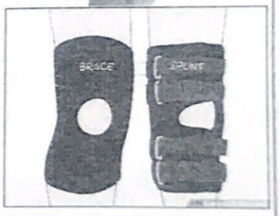

Synovium → Membrane of joint — عشان لما يانتجين من الادوية

Surgical Management

عملية استئصال لل Synovium بنعملها لما يكون عندي Two, one joint بس مصابين

- ✓ Corrective surgical procedures including synovectomy, total joint replacement, and joint fusion may be indicated in patients with RA to reduce pain and to improve function.
- ✓ Carpal tunnel syndrome is common, and surgical repair may be curative if local injection therapy is unsuccessful.

بطل في مفصل ما يتزبط لكل الأماكن يتزبط لل Wrist ، الابهام اما مثلاً الركبة لا ما يزبط

Medium nerve الي بعزي الايد من مفصل الـ Wrist بكون عليه ضغط الي بأدي لوجع

Live vaccines → ممكن اعطيها لل pt الي باخذوا Conventional DMARDs اما الـ Biologics & ما بصير

ازا بدنا نعطيها قبل ما نبلش بالـ Biologics وازا بعدهم لازم بعد ٣ اشهر من الانقطاع عن الدوا

Immunizations

- ✓ Live vaccines should not be given during treatment with biologics but instead should be given before starting therapy when possible and avoided for at least 3 months after immunosuppressants are discontinued.
- ✓ Live vaccines can be given to patients on methotrexate, leflunomide, sulfasalazine, and HCQ.
- ✓ Inactivated vaccines can be administered while patients are on conventional DMARDs, TNF and non-TNF biologics, and tofacitinib; however, efficacy of the vaccine may be reduced if patient is on methotrexate or biologic agents.
- ✓ Influenza and pneumococcal vaccinations should be considered for patients receiving DMARDs.
- ✓ Hepatitis B vaccination is recommended if risk factors for this disease exist and if hepatitis B vaccination has not previously been administered.

Complications

يكون التهاب واحد فالمفصل مقارنة بالمفاصل الباقين

- ✓ Patients with RA and a single joint inflamed out of proportion to the rest of the joints must be evaluated for coexistent septic arthritis. This complication occurs with increased frequency in RA and carries 20%– 30% mortality.

التهابات او ممكن بكتريا

- ✓ Approximately 70% of patients show irreversible joint damage on radiography within the first 3 years of disease. Work disability is common, and life span may be shortened.

- ✓ CV disease is accelerated in RA and is the commonest cause of death. RA is considered a CAD risk factor equivalent to diabetes and aggressive risk factor management should be instituted.

زي زي ال DM

- ✓ Sjögren syndrome, characterized by failure of exocrine glands, occurs in a subset of patients with RA, producing sicca symptoms (dry eyes and mouth), parotid gland enlargement, dental caries, and recurrent tracheobronchitis.

o Atoimmune disease

- ✓ Felty syndrome: The triad of RA, splenomegaly & granulocytopenia also occurs in a small subset of patients, & these patients are at risk for recurrent bacterial infections & nonhealing leg ulcers.

الاعضاء التكاثرية

عند ال Pt ← dry Mouth and eyes

لانه ال exocine الي بيفرز ال gland Saliva ، Tears بكون فيها impairment باثر على ال Visoin بحسو بالعين وزي رمل بعينهم. بكون عند هم صعوبه بالبلع والكلام.

عنده ٣ شغلان مع بعض

(1) RA (2) splenomegaly

(3) granulocytopenia = granulocytes in Blood بكون صار فيها depletion بتكون decreased

ازا مريض عنده صدود سوا معناها عنده Felty Syndro