APPROACH TO THE TREATMENT OF INFLAMMATORY POLYARTHRITIS

Notes by; Yara Aldigi

DR.AFSAR SAYEEDA, FRCP
CONSULTANT INTERNIST & RHEUMATOLOGIST
CTU – DEPARTMENT OF MEDICINE
KING KHALID UNIVERSITY HOSPITAL
KSUMC, RIYADH, KSA

CAUSES OF INFLAMMATORY POLYARTHRITIS

- **INFECTIONS - VIRAL/ BACTERIAL** (H PARVOVIRUS B19, CMV,CSV.HEPB.HIV,EBV,MUMPS,VZV ,ADENO.ENTERO.HHV)
- STAPH AUREUS, GONORRHOEA,GRAM NEGATIVE BACILLI Most common infections are Hep B and EBV
- **DIRECT/INDIRECT(REACTIVE ARTHRITIS-**SHIGELLA,SALMONELLA,CHLAMYDIA, YERSINIA,CAMPYLOBACTER,GROUP A STREPTOCOCCI, TROPHEREMA WHIPPELI ,WHIPPLES, INFECTIVE ENDOCARDITIS)

- **SYSTEMIC RHEUMATIC DISEASE –RA/SLE/AOSD/JRA**
- **CRYSTAL INDUCED ARTHRITIS -Gout / Pseudogout**
- **SYSTEMIC VASCULITIDES –HSP/PAN/WG**
- **SERONEGATIVE SPONDYLOARTHROPATHEIS - Psoriatic arthritis ,**
  IBD related (enteropathic) ,
  Reactive arthritis &
  Ankylosing Spondylitis is the most imp

INFLAMMATORY VS NONINFLAMMATORY

INFLAMMATORY

- **MORNING STIFFNESS OF MORE THAN AN HOUR**
- **LOW GRADE TEMPERATURE, FATIGUE, SKIN RASH**
- **SIGNS OF INFLAMMATION- RUBOR (REDNESS)**
- **WARMTH(CALOR). SWELLING(*EFFUSION-TUMOUR), TENDERNESS(DOLOR) LOSS OF FUNCTION.**
- **LABS –ESR, CRP ,ANAEMIA OF CHRONIC DISEASE, RF, ANTICCP, ANA….** Normocytic normochromic anemia
- **X RAYS- EROSIONS, UNIFORM JOINT SPACE NARROWING.** the entire cartilage is destroyed/ destructed from medial and lateral side
- **SYNOVIAL FLUID ANALYSIS -> 2000(NONINFECTIOUS), > 50000(INFECTIOUS)PREDOMINANTLY NEUTROPHILS.**

* the effusions in inflammatory diseases may appear like a tumor but are not a true tumor

NONINFLAMMATORY

- **LESS THAN AN HOUR**

- the swelling is bony not fluid

- **BONY PROLIFERATION – HEBERDENS NODES, BOUCHARDS NODES)**

- no signs of inflammation like rubor etc

- **NORMAL LABS**
- ***JOINT SPACE NARROWING, SUBCHONDRAL SCLEROSIS,OSTEOPHYTES .**
- **SYNOVIAL FLUID < 200 CELLS 50% NEUTROPHILS**

* joint space narrowing occurs in the medial compartments due to weight-bearing (degenerative)

RHEUMATOID ARTHRITIS

- ACUTE AND CHRONIC INFLAMMATION IN SYNOVIUM CAUSING PROLIFERATION AND DESTRUCTION OF JOINT TISSUES.

(Disease Modifying Anti-Rheumatic Drugs)

- TO ACHIEVE THE BENEFITS OF INTERVENTION WITH EARLY DMARDS DEPENDS THE DIAGNOSIS OF RA AS EARLY AS POSSIBLE.

- RECOGNISE RA EARLY BEFORE IRREVERSIBLE JOINT INJURY OCCURS.

THE GOALS OF RA TREATMENT ARE TO:

- **STOP INFLAMMATION(PUT DISEASE IN REMISION)**

- **RELEIVE SYMPTOMS**

- **PREVENT JOINT AND ORGAN DAMAGE**
  mainly affects the lung, heart, eye

- **IMPROVE PHYSICAL FUNCTION AND OVERALL WELLBEING**
  due to the pain they wont function well and it will cause long-term absences

- **REDUCE LONG TERM COMPLICATIONS**
  such as deformities; which are of functional and cosmetic importance

NONPHARMACOLOGIC THERAPIES

- **PATIENT EDUCATION** and specific advices given by a rheumatologist
- **REST,EXERCISE,PHYSICAL AND OCCUPATIONAL THERAPY**
- **NUTRITIONAL AND DIETARY COUNSELLING** for ex. in Gout you'd advice to decrease protein intake
- **INTERVENTIONS TO DECREASE THE* CV RISKS, eg: SMOKING CESSATION**
- **IMMUNISATIONS TO DECREASE THE INFECTIOUS COMPLICATIONS OF IMMUNOSUPPRESSIVE THERAPIES.**

* you address the disease (RA/SLE) and other comorbidities such as HTN, DM, Hyperlipidemia

Pretreatment evaluation

Prior to starting, resuming, or significantly increasing therapy with nonbiologic or biologic DMARDs, we do the following baseline studies :

- General testing for all patients —CBC, s. creatinine, AT, ESR, & CRP. used for disease activity
- Serologic testing for hepatitis prior to **methotrexate , leflunomide**, or biologic DMARDs —* (*All patients at increased risk of hepatitis, such as those who have a history of iv drug abuse, multiple sex partners in the previous 6 mnths, and those who are healthcare workers, should be screened for hepatitis B and C before starting these medications*) * they are more prone and should be screened before giving medication
- Ophthalmologic screening for **hydroxychloroquine** use .
- Testing for latent tuberculosis —skin testing or an interferon-gamma release assay prior to all biologic DMARDs and prior to use of the Janus kinase inhibitor, **tofacitinib**. ppd and quantiferon are the gold standard fot testing

Choice of therapy

- Rapidly acting antiinflammatory medications, including nonsteroidal antiinflammatory drugs (**NSAIDs**) and systemic and intraarticular **glucocorticoids**.
- **Nonbiologic DMARDs** : hydroxychloroquine , sulfasalazine , methotrexate , and leflunomide .
- **Biologic DMARDs:** produced by *recombinant DNA technology*, generally *target cytokines or their receptors* or are directed against other cell surface molecules.
- **Several kinase inhibitors** : **Tofacitinib** . It is an orally administered small molecule DMARD that inhibits cytokine and growth factor signalling *through interference with Janus kinases.*
- **Denosumab** in Osteoporosis

you need to know the meds for osteoporosis and their complications

Note: Ruxolitinib is used in Polycythemia Vera

Table 1. Summary of Nonbiological DMARDs for Rheumatoid Arthritis

these 3 are hardly used anymore

Drug	Usual Maintenance Dosage	Approximate Time for Benefit
Azathioprine	1-2.5 mg/kg/day divided over 2-4 doses. After 4 wk, may increase by 0.5 mg/kg/day every 4 wk	2-3 mo
D-penicillamine	250-750 mg/day	3-6 mo
Gold	Oral: 3 mg twice daily IM: 25-50 mg every 2-4 wk	4-6 mo 3-6 mo
Hydroxychloroquine	200 mg twice daily	2-6 mo
Leflunomide	100 mg daily for 3 days then 20 mg per day	4-12 wk
Methotrexate	Oral/injectable: 7.5-20 mg/wk	1-2 mo
Sulfasalazine	1,000 mg 2-3 times daily	1-3 mo

IM: intramuscular; DMARDs: disease-modifying antirheumatic drugs.
Source: References 10, 14.

you should know the side effects of all the medications for MCQ and daily practice

NonBiologic DMARDs

MTX; is used commonly as a weekly dosage unlike other medications, you should monitor hepatic function. takes 1-2 months to cause relief

Names	Major Adverse effect
Hydroxychloroquine MC	damage to the retina of the eye
Sulfasalazine best effect within 3m	nausea, vomiting, loss of appetite, headache, dizziness, may cause skin and urine to turn orange-yellow. hepatitis
methotrexate	Rash liver/lung, bone marrow toxicity
Leflunomide	Diarrhea, activates latent tb, not used
Azathioprine	nausea, vomiting, decreased appetite, liver function abnormalities, low white blood cell counts
Cyclosporine	HTN, Renal dysfunction

* HCQ: takes 3-6 month to cause relief so give a bridging therapy such as Nsaids or steroids. it causes bulls eye macula disease & it also acts on DHEA enzyme and causes folate deficiency (Macrocytic anemia) and BM disease with long term use

Biologic DMARDs

remember the biologic DMARDS name and examples
a mnemonic to help EATAR

Names	Examples
TNF Inhibitor — it can be given all throughout pregnancy but once the babys delivered its vaccinations need to be delayed and pedia team should be informed	Etanercept, Golimumab, Adalimumab and Certolizumab, Infliximab (E-GACI)
IL1 Antagonist	Anakinra — best used in AOSD
IL-6 receptor antagonist	Tocilizumab — its monotherapy doesnt require MTX unlike other biologic meds (advantage)
T-cell costimulation blocker	Abatacept
Anti-CD20 B-cell depleting monoclonal antibody	Rituximab — used in oncology and RA

Janus kinase inhibitors, JAK inhibitors or jakinibs

can be given as IV by the physician or subQ self injection

- are a type of medication that functions by **inhibiting** the activity of one or more of the **Janus kinase** family of enzymes (JAK1, JAK2, JAK3, TYK2), thereby interfering with the **JAK**-STAT signaling pathway.
- In contrast to **biologic** therapies, which are large proteins that require injecting and are incapable of penetrating the lipid bilayer cell membrane, **JAK inhibitors** are small molecules that are orally available and can cross the cell membrane to block activity of one or more cytoplasmic JAKs. a major advantage over other meds
- Are immunosuppressants

- JAK inhibitors belong to a family of **DMARDs**
- Three JAK inhibitors, **baricitinib** (**Olumiant**),**tofacitinib**(**Xeljanz**), and **upadacitinib** (Rinvoq), are approved by the FDA to treat rheumatoid arthritis.

- **Tofacitinib**, a first-generation jakinib that inhibits JAK3, JAK1, and to a lesser degree **JAK2**, is the first jakinib developed for the treatment of autoimmune disease.
- Barcitinib – the second JAK inhibitor approved for RA (INHIBITS jak 1 and 2) **.**
- **Upadacitinib** (ABT-494) is a JAK1 selective inhibitor being investigated to treat rheumatoid arthritis, Crohn's disease, ulcerative colitis, atopic dermatitis, psoriatic arthritis, axial SpA and Giant Cell Arteritis and Takayasu Arteritis.

you dont need to go into too much detail

BIOSIMILARS

A **biosimilar** is a biologic medical product (also known as biologic) highly similar to another already approved biological medicine (the 'reference medicine')

for example infliximab has a biosimilar which is not yet used in practice

Early use of DMARDs : stratification

mildly active RA
moderately to severely active RA,
resistant to initial DMARD therapy (eg, MTX)

DEFINITION OF MILDLY ACTIVE RA

Patients with mildly active rheumatoid arthritis (RA) typically meet *ACR/EULAR criteria for RA* and have all of the following

1. Fewer than five inflamed joints
2. Mildly elevated or normal ESR and C-rp levels
3. No extraarticular disease
4. No evidence of erosions/cartilage loss on radiographs of the hands, wrists, and feet
5. Low levels of measures of disease activity such as the DAS28

DAS28 is an app used to monitor disease activity

DEFINITION OF MODERATELY TO SEVERELY ACTIVE RA

- Patients with moderately to severely active RA are at greater risk of developing joint damage and disability than patients with mildly active disease . These patients typically meet the *American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) criteria for RA* and exhibit a combination of the following: these indicate a bad prognosis

1. At least **5 inflamed joints**
2. **Elevation in the ESR** and/or serum CRP concentration
3. **Positive RF** and/or anticyclic citrullinated peptide (CCP) antibodies
4. **Evidence of inflammation** on plain radiography of the hands, wrists, or feet, such as osteopenia and/or periarticular swelling. In addition, minimal joint space narrowing and small peripheral erosions may be observed.

Definition of resistance to initial DMARDs

Resistance to initial DMARD therapy is defined as one of the following:

- **Failure to achieve remission or low disease activity** within 3-6 mnths of initiating (MTX) or other DMARD therapy in maximally tolerated doses.
- A requirement, in addition to DMARDs, for **chronic glucocorticoid therapy** in a dose of greater than about 5-7.5 mg/day of **prednisone** or equivalent to achieve or maintain remission or low disease activity after 3-6 mnths of Rx with DMARDs.
- **A requirement for multiple courses with glucocorticoids**, in excess of doses used for chronic therapy, for the treatment of recurrent disease flares.

- **USE OF ANTIINFLAMMATORY THERAPY,INCLUDING NSAIDS & GLUCOCORTICOIDS IS TO HELP CONTROL THE SYMPTOMS & IMPROVE FUNCTION UNTIL DMARDS TAKE EFFECT.**

if you gave a full dose of immunosuppressive med and it didnt work you can give a low dose of steroids to help cope

- **ACHEIVEMENT AND MAINTENANCE OF TGHT CONTROL OF DISEASE ACTIVITY , DEFINED AS REMISSION OR A STATE OF LOW DISEASE ACTIVITY.**

Early use of DMARDs

mildly active RA clinical sx but no inflammatory markers	**Initiate antiinflammatory therapy with a NSAID for rapid symptomatic relief and begin DMARD treatment with either hydroxychloroquine (HCQ) or sulfasalazine (SSZ).**
moderately to severely active RA,	Initiate antiinflammatory therapy with either a NSAID or glucocorticoid, and generally start DMARD therapy with methotrexate (MTX).
resistant to initial DMARD therapy (eg, MTX) - it fails to remit within a 3-6m margin - > 3-6m use of CS - multiple CS use	treat with a combination of DMARDs (eg, MTX plus either a TNF inhibitor or SSZ and HCQ) or, alternatively, we switch the patient to a different DMARD of potentially comparable efficacy (eg, leflunomide or a TNF inhibitor), while also treating the active inflammation with antiinflammatory drug therapy.

Rheumatoid arthritis

Mild

NSAIDs or hydrochloroquine

Moderate/severe

Non-biologic DMARDs
methotrexate, hydroxychloroquine, sulfasalazine
(combinations with MTX recommended)

TNF α-blockers
etanercept, adalimumab or infliximab

B-cell depleting therapy

2016 EULAR Recommendations -12

- Patients with active disease should be monitored every 3 months, and treatment should be adjusted if there is no improvement at 6 months
- Methotrexate (MTX) is recommended as first-line therapy; sulfasalazine (SSZ) or* leflunomide can be substituted if there are contraindications to MTX or they dont have access to other meds
- Tumor necrosis factor (TNF) inhibitors are no longer the only biologics recommended for patients with an insufficient response to MTX; all biologics are considered to be similarly effective
- Biologics should be combined with disease-modifying antirheumatic drugs (DMARDs)

* if they cant tolerate lefluno orally due to N/V > give subQ if they cant tolerate > take them off medication

Disease Activity	Recommendations
Early RA (<6 months) **(Notable change from 2012 to 2015 guidelines: The 2015 guidelines do not recommend initial combination DMARD therapy in early RA with moderate to high disease activity)**	• Administer DMARD monotherapy in patient with low-high disease activity • If disease activity remains moderate /high despite DMARD monotherapy, use combination DMARDs or a TNF inhibitoror a non-TNF biologic use 3 medications at once and once it remits take one off
Established RA (=6 month or meets 1987 ACR RA classification criteria)	If disease activity remains moderate or high despite DMARD monotherapy, ACR guidelines recommend one of the following: • Combination DMARDs • Add an anti-TNF biologic • Non-TNF biologic • Tofacitinib
If disease activity remains moderate or high despite use of a single anti-TNF biologic:	• Switch to a non-TNF biologic with or without MTX over another anti-TNFi or Tofacitinib
If disease activity remains moderate or high despite use of one anti-TNF biologic and one non-TNF biologic:	• Use another non-TNF biologic with or without MTX over Tofacitinib • If still uncontrolled use Tofacitinib
(Notable change from 2012 to 2015 guidelines: Instead of switching from one anti-TNF biologic to another anti-TNF biologic because of continued activity, it is recommended to change first to a non-TNF biologic)	

2015 ACR Guideline for the Treatment of RA

Monotherapy: Methotrexate or leflunomide recommended for all patients regardless of disease duration or severity

Dual-DMARD combinations: Methotrexate and hydrcosychloroquine recommended for moderate-to-high disease activity; Methotrexate or leflunomide with longer disease duration.

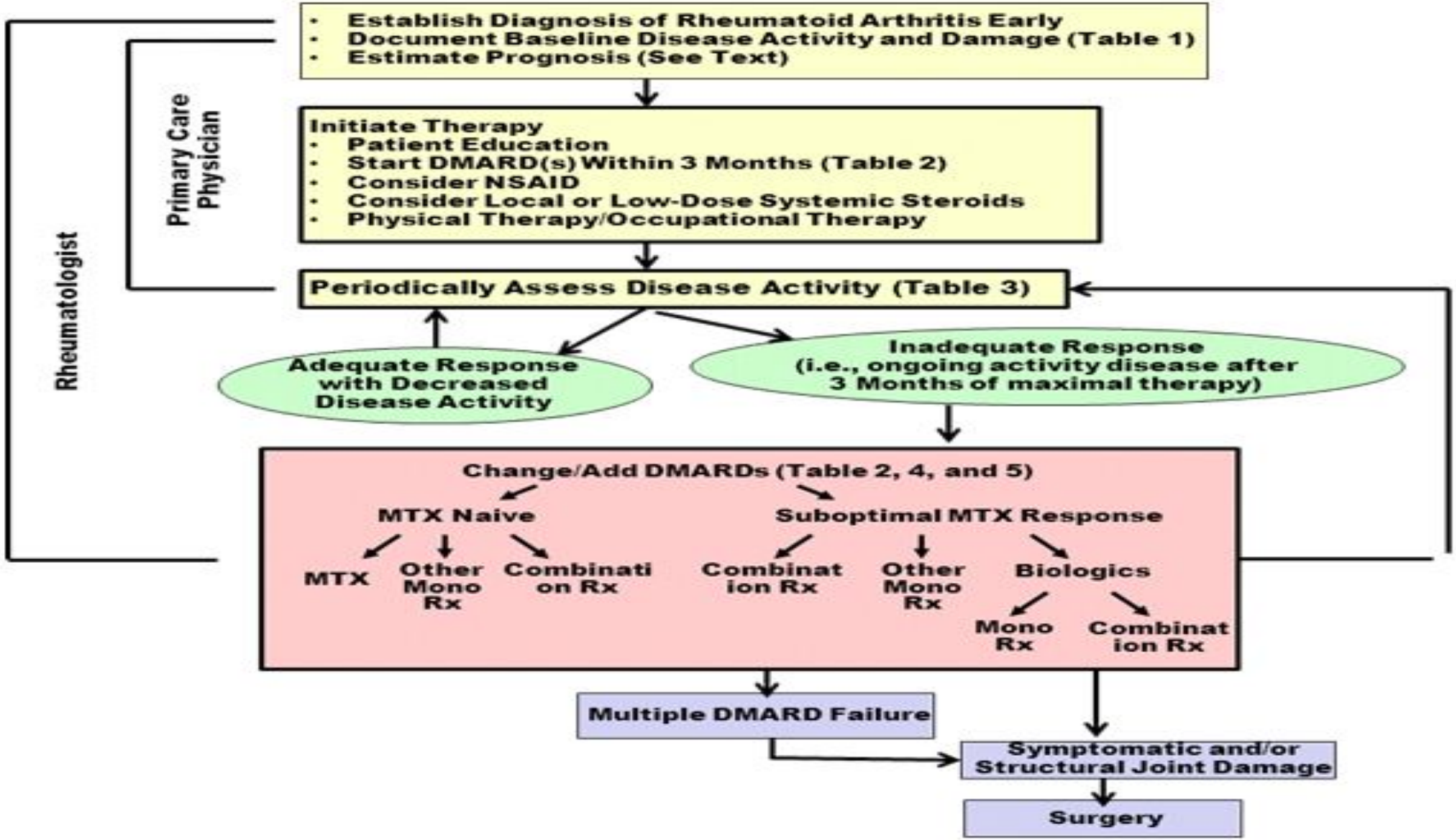
Triple-DMARD combinations: Methotrexate,sulfasalazine and hydrcosychloroquine recommended for patients with poor prognostic features and moderate-to-high levels of disease activity.

Anti-TNF-alpha agents: Etanercept, infliximad, adalimumab plus methotrexate recommended for patients with early RA(symptoms <3 months) with high disease activity and no history of ever being treated with DMARD. TNF blockers are recommended fo a long disease duration and for those patients who failed to obtain a satisfactory response from methotrexate therapy.

Abatacept or rituximab recommended for patients with at least moderate disease activity and poor prognostic indicators following treatment with methotrexate or other DMARDs resulting in inadequate treatment response

ACR-American College of Rheumatology; DMARDs- Disease-modifying antirheumatic drugs; RA – rheumatoid arthiritis; TNF – Tumor necrosis factor

-Poor prognosis features include high number of affected joints, pra--- of bonyerosioes, elevated theumatoid factor for C-reactive protein, anticycle


Rheumatologist
Primary Care Physician
• Establish Diagnosis of Rheumatoid Arthritis Early
• Document Baseline Disease Activity and Damage (Table 1)
• Estimate Prognosis (See Text)
Initiate Therapy
• Patient Education
• Start DMARD(s) Within 3 Months (Table 2)
• Consider NSAID
• Consider Local or Low-Dose Systemic Steroids
• Physical Therapy/Occupational Therapy
Periodically Assess Disease Activity (Table 3)
Adequate Response with Decreased Disease Activity
Inadequate Response (i.e., ongoing activity disease after 3 Months of maximal therapy)
Change/Add DMARDs (Table 2, 4, and 5)
MTX Naive
Suboptimal MTX Response
MTX
Other Mono Rx
Combination Rx
Combination Rx
Other Mono Rx
Biologics
Mono Rx
Combination Rx
Multiple DMARD Failure
Symptomatic and/or Structural Joint Damage
Surgery

PROGNOSIS

the delay will lead to deformities

- **OUTCOME IN RA IS COMPROMISED WHEN DIAGNOSIS AND TREATMENT ARE DELAYED.**

not all patients are the same, you should judge based on good/bad prognostics during diagnosis of the disease

- **OUTCOMES ARE HIGHLY VARIABLE.SOME PATIENTS EXPERIENCE A RELATIVELY SELF LIMITING DISEASE WHILE OTHERS HAVE A CHRONIC PROGRESSIVE ILLNESS.**

some feel relief with nsaids and HCQ only, some need biological therapy and others are on b-cell depleting meds and still cant reach complete remission

- **40% OF THE PATIENTS BECOME DISABLED AFTER 10 YEARS.**

- **INTERVENTIONS WITH DMARDS IN VERY EARLY RA(SYMPTOM DURATION OF LESS THAN 12 WEEKS AT THE TIME OF FIRST TREATMENT) GIVES THE BEST OPPURTUNITY FOR ATTEMPTING TO ACHIEVE DISEASE REMISSION.**

UNFAVOURABLE PROGNOSTIC FACTORS

- **HLA DR4 GENOTYPE**
- **HIGH SERUM TITER OF AUTOANTIBODIES(RF & ACPA)**
- **PRESENCE OF EXTRAARTICULAR MANIFESTATIONS**
- **LARGE NUMBER OF INVOLVED JOINTS**
- **AGE YOUNGER THAN 30 YEARS**
- **FEMALE SEX**
- **PRESENCE OF SYSTEMIC SYMPTOMS**

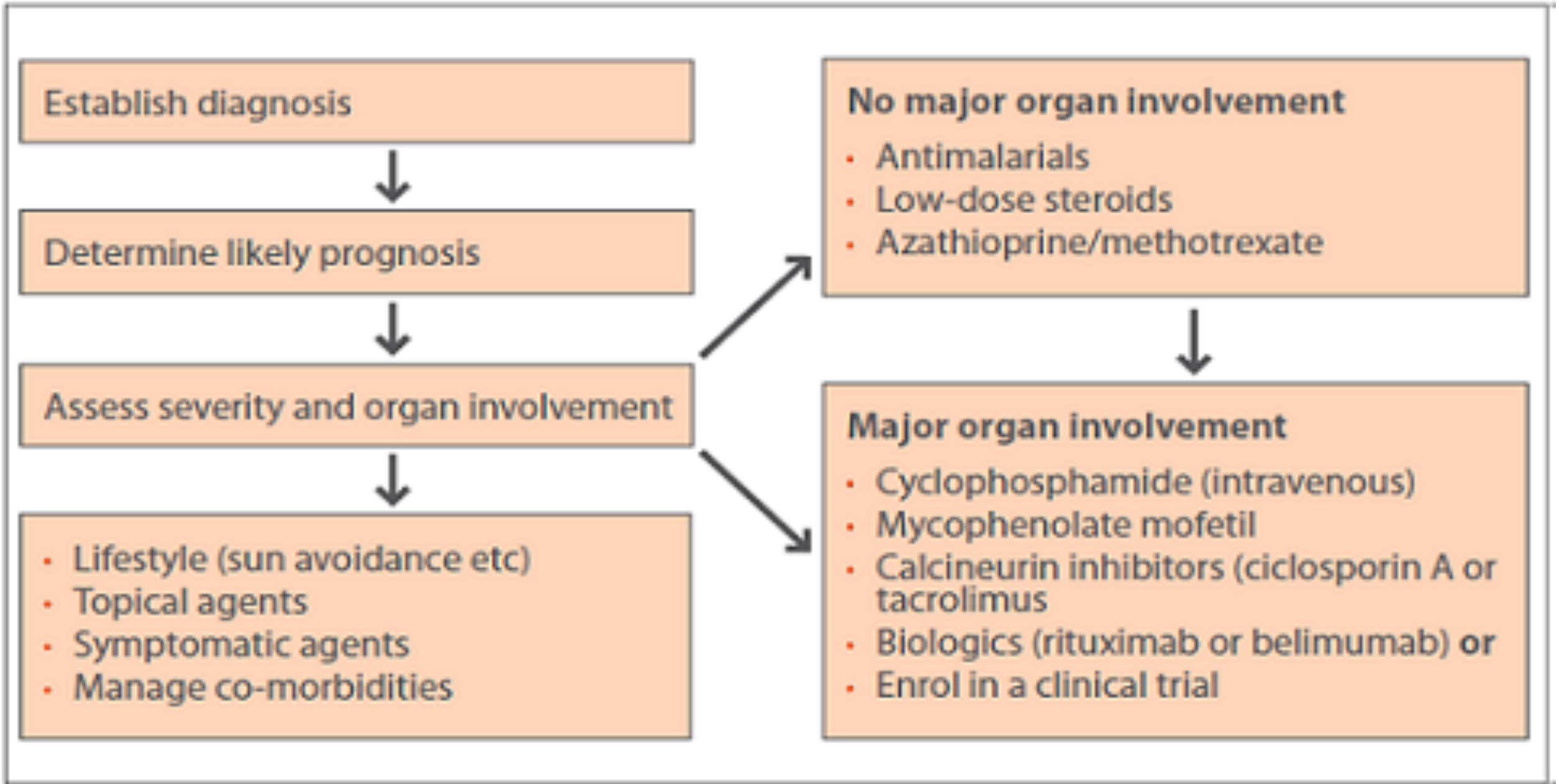
SYSTEMIC LUPUS ERYTHEMATOSUS

- MANAGEMENT DEPENDS ON DISEASE SEVERITY AND DISEASE MANIFESTATIONS.
- HYDROXYCHLOROQUINE HAS A CENTRAL ROLE FOR LONG TERM TREATMENT IN ALL PATIENTS.

  DECREASES NUMBER OF FLARES AND PROLONGS LIFE by keeping them in remission

  CORNERSTONE OF SLE MANAGEMENT due to its few s/e

- **SLE WITH ARTHRITIS – NSAIDS, HCC, short courses of STEROIDS.** and MTX



Overview of the management of systemic lupus erythematosus.

AOSD

it is a systemic variant of juvenile idiopathic arthritis that occurs in those > 16y.
it presents as lymphadenopathy, fever, arthritis, hepatosplenomegally (IMP to exclude malignancy and infection)

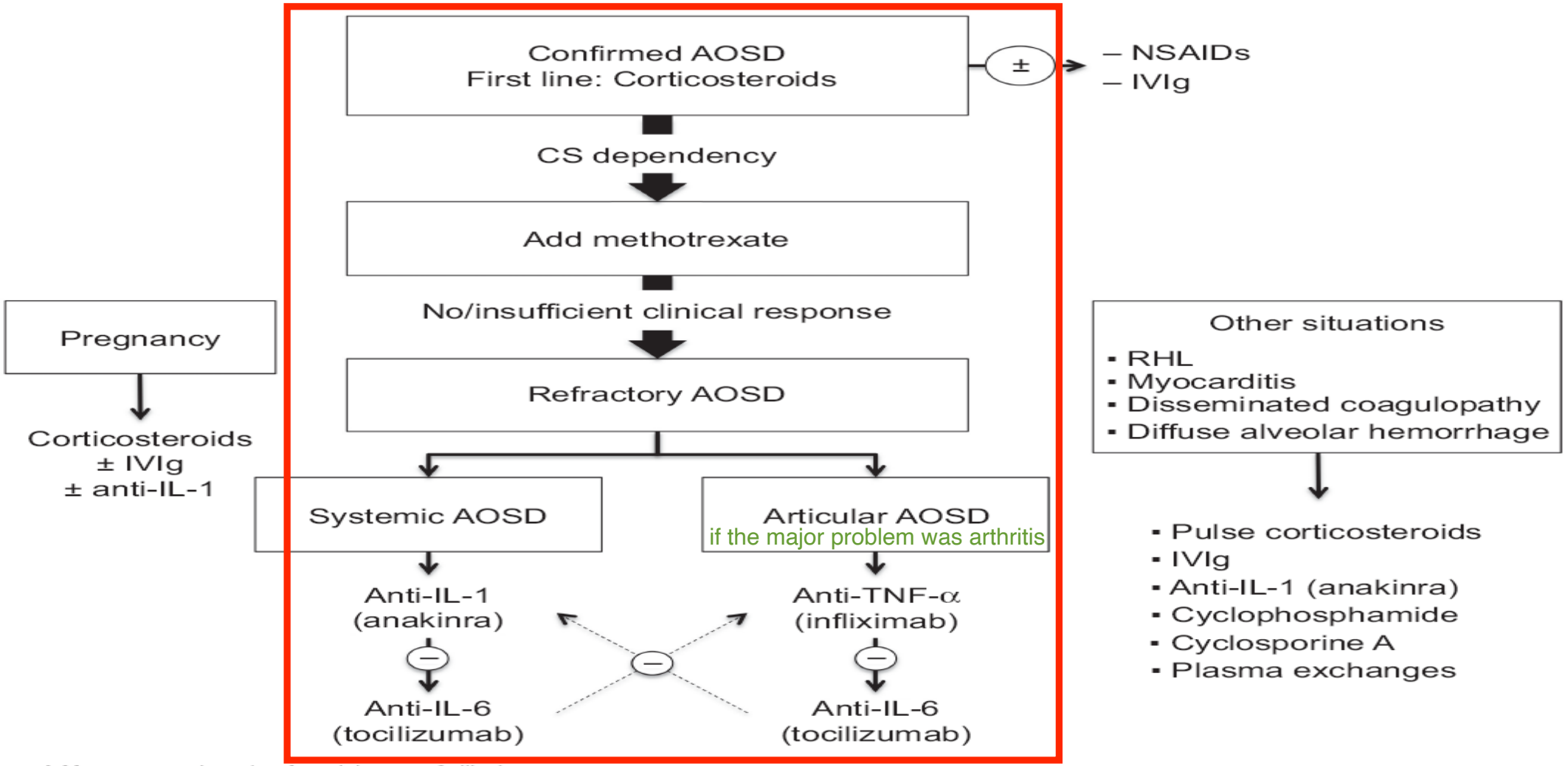
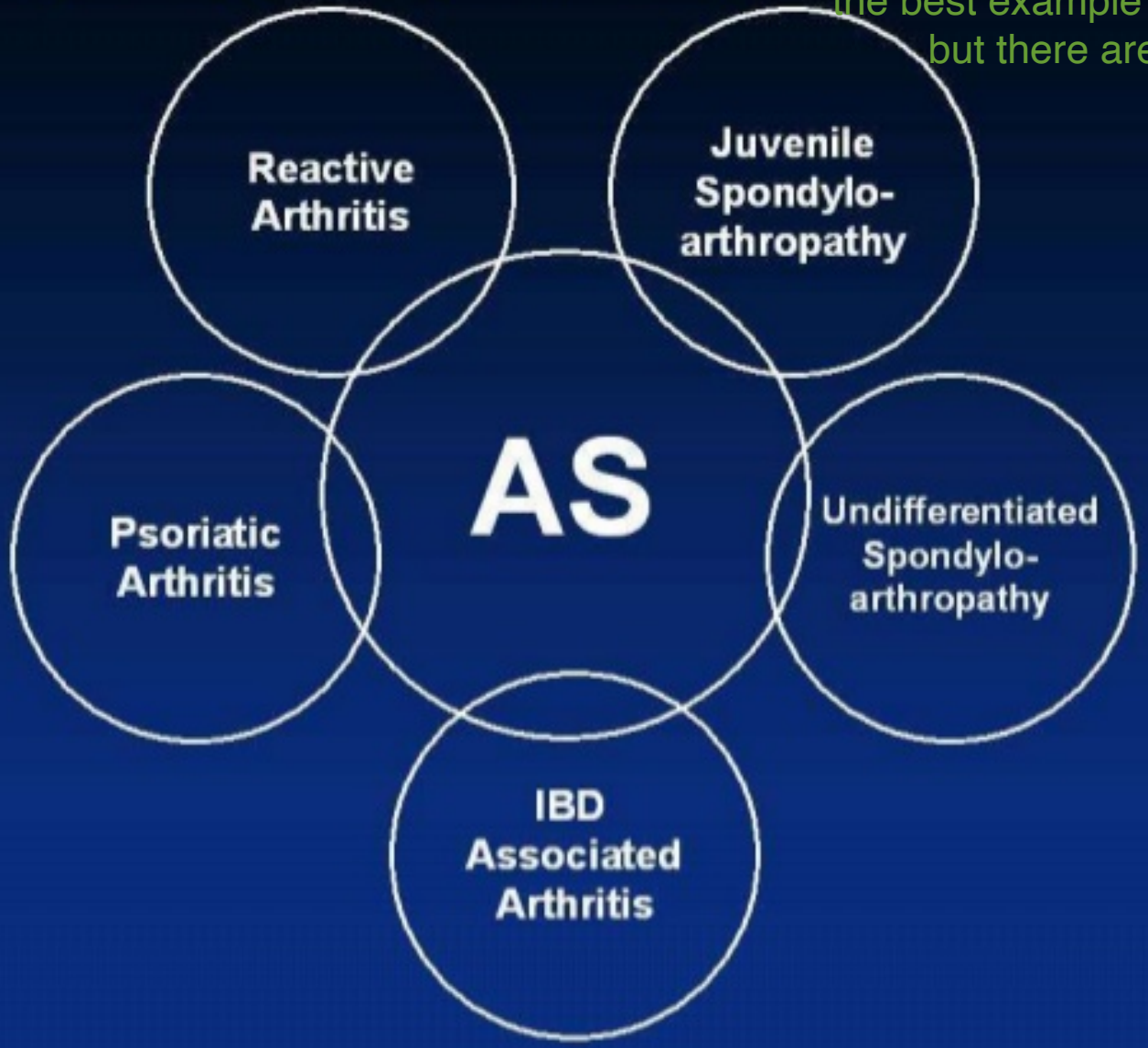


Figure 1 Management algorithm for adult-onset Still's disease.
Abbreviations: AOSD, adult-onset Still's disease; CS, corticosteroids; IVIg, intravenous immunoglobulin; NSAIDS, nonsteroidal anti-inflammatory drugs; RHL, reactive hemophagocytic lymphohistiocytosis.

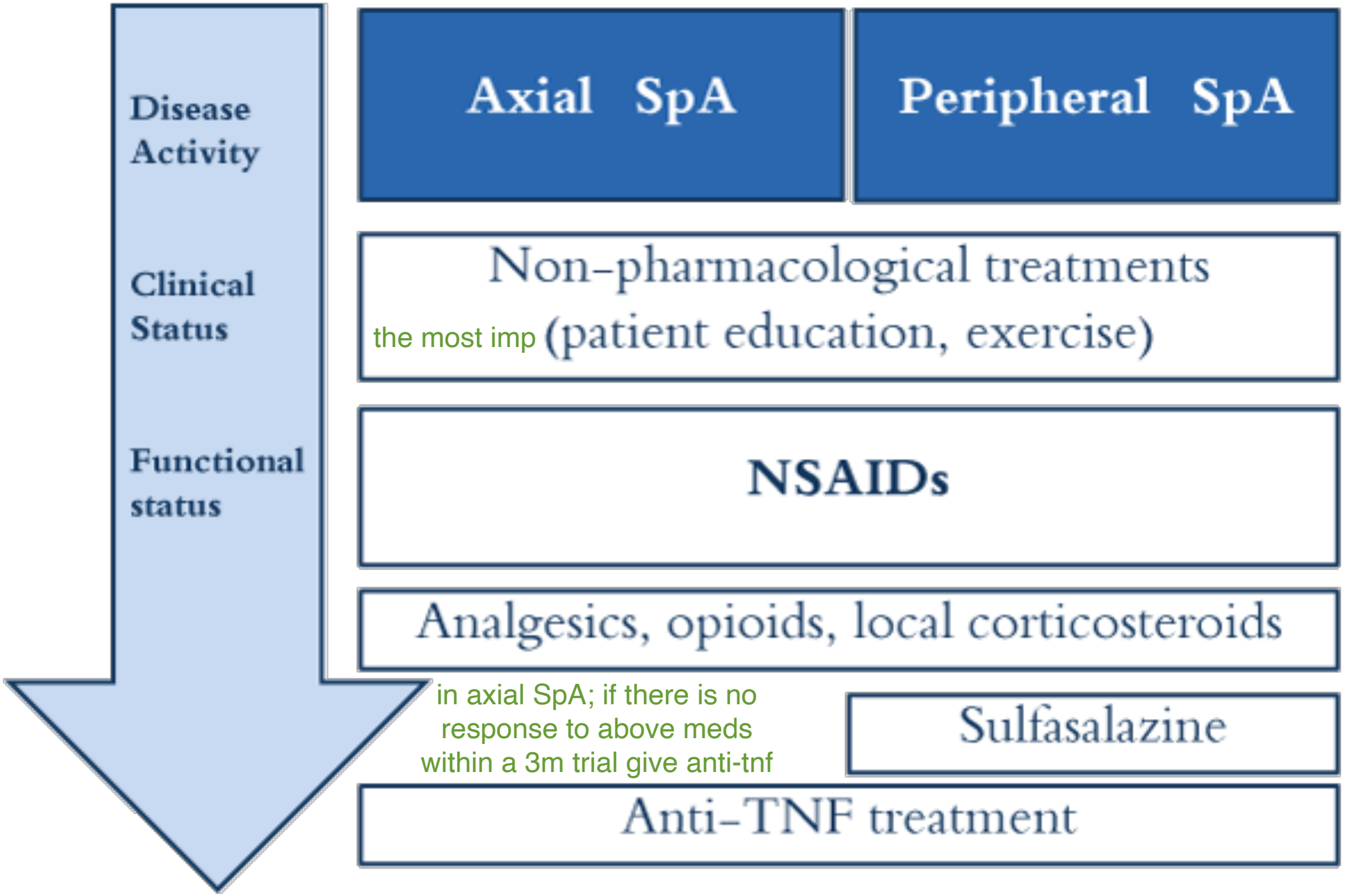
Family of Spondyloarthropathies

the best example would be AS
but there are others



Seronegative Spondyloarthropathies

- Seronegative (test negative for RF)
- Presence of HLA B27 (Class I)
- Inflammation of the sacroiliac joint and spine
- Enthesitis: Inflammation at insertion sites of tendon or ligament to bone
- Asymmetric Inflammatory Arthritis unlike RA which is symmetric
- Extrarticular Disease


Disease Activity
Clinical Status
Functional status
Axial SpA
Peripheral SpA
Non-pharmacological treatments
the most imp (patient education, exercise)
NSAIDs
Analgesics, opioids, local corticosteroids
in axial SpA; if there is no response to above meds within a 3m trial give anti-tnf
Sulfasalazine
Anti-TNF treatment

in LM they show up as yellow needle shaped crystals that are negatively birefringent

more in men and post-menopausal women
affects both small and large joints

Gout Treatment Options

Acute Gout

NSIADs
like diclofenac or ibuprofen

Colchicine
give for 20min till you either get relief or s/e begin to show

Steroids
if its just one joint give intra-articular if more give IM

Prevention of Recurrent Attacks

Modify risk factors
Obesity, Die, Alcohol, Diuretics, HTN

Uricosuric Agents
Probenecid, Sulfinpyrazole

Xanthine oxidase inhibitors
(can precipitate acute attacks so needs prophylaxis with NSAIDs/Colchicine/ Steroids)
Allopurinol Febuxostat

allo is used most commonly unless they have renal impairment then use Febu

Renal Failure must prompt caution with NSAIDs, Colchicine, Probenecid, Sulfinpyrazole and Allopurinol

Pseudogout

more in those >50y
affects women and men
may be secondary to hyperparathyroid,hemochromatosis

- Treatment
  - Avoid joint overuse
  - NSAIDs
  - Colchicine, though less effective than in acute gout
  - Synovial fluid aspiration
  - Intra-articular steroids
  - No proved effective agents to dissolve CPPD crystals
  - Joint replacement in destructive disease, with symptoms resistant to drugs

calcium pyrophosphate dihydrate crystals

in arthrocentesis they show up as blue rhomboid-shaped crystals that are positively birefringent

THANK YOU