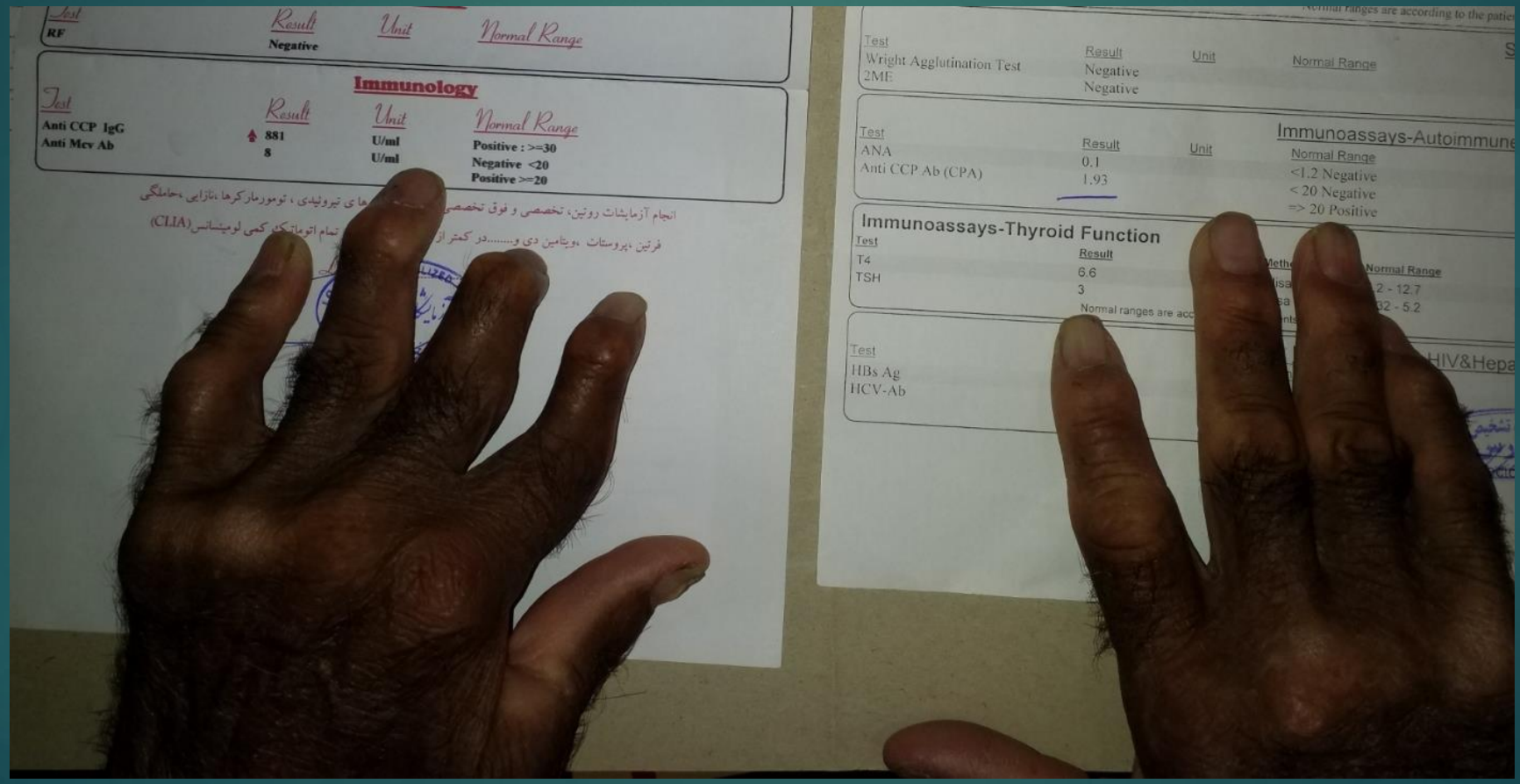
بنام خدا

Evaluation and Management of Rheumatoid Arthritis

Rheumatoid Arthritis: Treatment Principles

- **Confirm** the diagnosis
- **Determine where** the patient stands in the spectrum of disease
- When damage begins early, **start aggressive** treatment early
- Use the **safest treatment** plan that matches the aggressiveness of the disease
- **Monitor treatment** for adverse effects
- **Monitor disease activity**, revise Rx as needed



Test	Result	Unit	Normal Range
RF	Negative		

Immunology

Test	Result	Unit	Normal Range
Anti CCP IgG	↑ 881	U/ml	Positive : >=30
Anti Mcv Ab	8	U/ml	Negative <20 Positive >=20

انجام آزمایشات روتین، تخصصی و فوق تخصصی ... های تیروئیدی ، تومورمارکرها ،نازایی ،حاملگی

فرتین ،پروستات ،ویتامین دی و.....در کمتر از ... تمام اتوماتیک کمی لومینسانس(CLIA)

Test	Result	Unit	Normal Range
Wright Agglutination Test	Negative		
2ME	Negative		

Immunoassays-Autoimmune

Test	Result	Unit	Normal Range
ANA	0.1		<1.2 Negative
Anti CCP Ab (CPA)	1.93		< 20 Negative => 20 Positive

Immunoassays-Thyroid Function

Test	Result	Normal Range
T4	6.6	...2 - 12.7
TSH	3	...32 - 5.2

Normal ranges are acc...

Test
HBs Ag
HCV-Ab

...HIV&Hepa...

Factors Associated With Poor Prognosis in Rheumatoid Arthritis

- Presence of rheumatoid factor and titer
- Presence of antibodies to CCP and titer
- Presence of shared epitope and number of alleles
- Presence of erosive disease at presentation
- Disease activity at presentation
- Magnitude of ESR or CRP elevations
- Presence of nodules or extraarticular features
- Female gender
- Smoking currently and in the past
- Obesity

American College of Rheumatology/European League Against Rheumatism **Definitions of Remission in Rheumatoid Arthritis** Clinical Trials

- **Boolean-Based Definition**

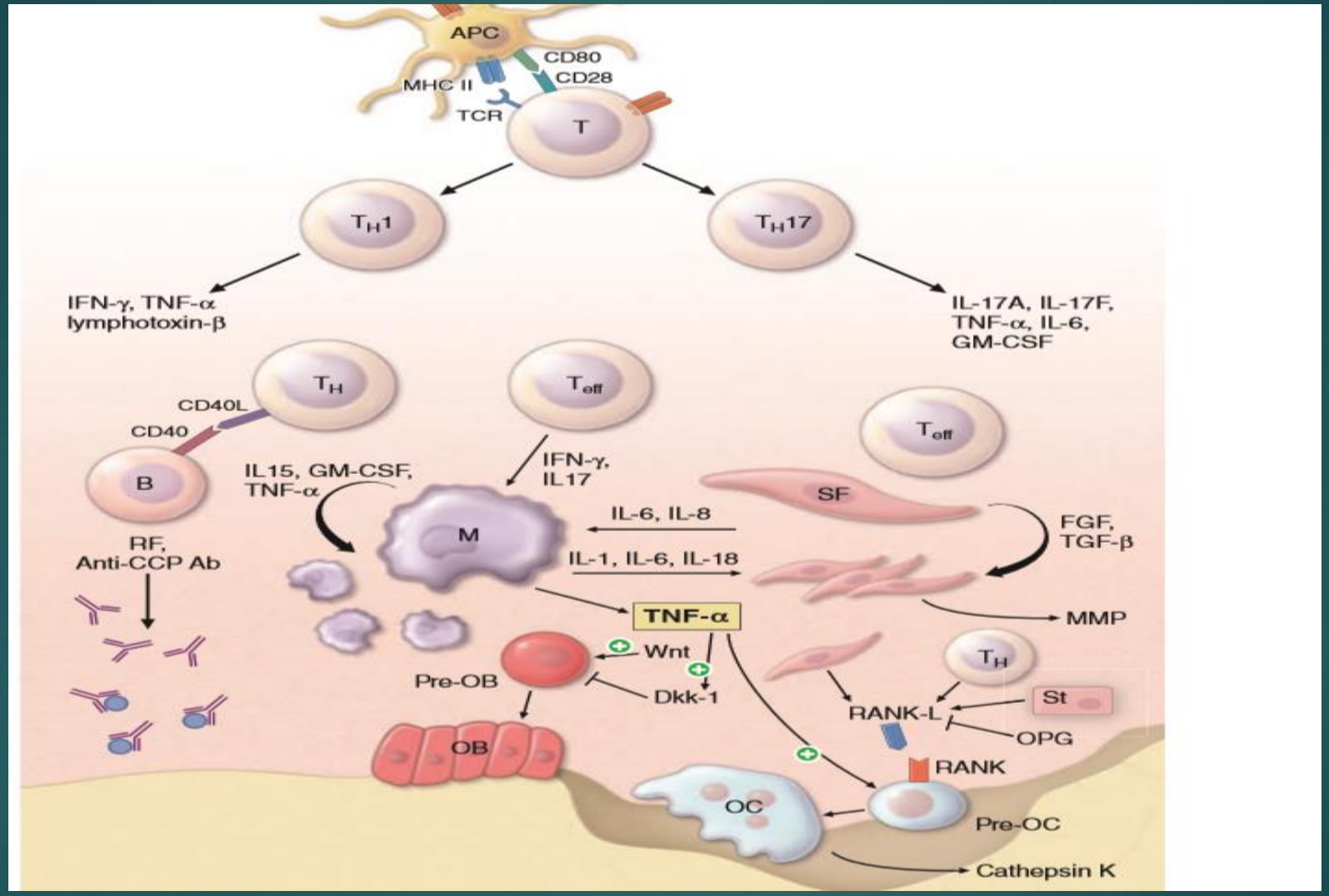
At any time point, the patient must satisfy all of the following:

- Tender joint count ≤1*
- Swollen joint count ≤1*
- C-reactive protein ≤1 mg/dL
- Patient global assessment ≤1 (on a 0-10 scale)

Index-Based Definition At any time point, the patient must have a Simplified Disease Activity Index score of **≤3.3**.

Evaluation and Management of Rheumatoid Arthritis

- **Main treatment goals** are to control disease activity and slow the rate of joint damage, in addition to minimizing pain, stiffness, inflammation, and complications.
- Pharmacologic therapies that are used include:
- **nonbiologic** and **biologic DMARDs** and
- adjunctive agents such as **corticosteroids, NSAIDs**, and analgesics.


APC
CD80
CD28
MHC II
TCR
T
T_H1
T_H17
IFN-γ, TNF-α
lymphotoxin-β
IL-17A, IL-17F,
TNF-α, IL-6,
GM-CSF
T_H
CD40L
CD40
B
RF,
Anti-CCP Ab
IL15, GM-CSF,
TNF-α
T_{eff}
IFN-γ,
IL17
M
IL-6, IL-8
IL-1, IL-6, IL-18
SF
FGF,
TGF-β
MMP
TNF-α
Wnt
Dkk-1
Pre-OB
OB
T_H
St
RANK-L
OPG
RANK
OC
Pre-OC
Cathepsin K

Disease-Modifying Anti-rheumatic Drugs(DMARD)

Conventional DMARD

- Hydroxychloroquine (HCQ)
- Azathioprine (AZA)
- SSZ
- MTX
- Leflunomide
- Cyclosporine
- Gold salts
- D-penicillamine
- Minocycline

Biologic DMARD

- Etanercept
- Infliximab
- Adalimumab
- Certolizumab
- Golimumab

- Rituximab
- Tocilizumab
- Abatacept
- Anakinra

Evaluation and Management of Rheumatoid Arthritis

- DMARDs represent the **most important** measure in the successful treatment of RA.
- These agents can **retard or prevent** disease **progression** and, thus, **joint destruction** and subsequent **loss of function**.
- **Successful DMARD therapy :**until the full action of DMARDs takes effect, **anti-inflammatory or analgesic medications** may be required as **bridging therapy** to **reduce pain and swelling**.

Nonbiologic DMARDs

- The results of a retrospective cohort study found that the use of **HCQ** may **decrease the risk of diabetes** in patients with RA.
- **MTX and SSZ** are the **most active compounds** and provide the best risk-benefit ratios.
- **MTX**, **either alone or in combination** with other agents, has become the standard of care for **moderate to severe RA**.
- Injectable **gold salts** and **penicillamine rarely** induce sustained remission and thus have largely been supplanted by more effective agents.

Nonbiologic DMARDs

- In a meta-analysis of 158 trials, **triple therapy** (MTX, SSZ, and HCQ) was found to have a statistically **significant benefit** of inhibiting joint damage compared with **oral MTX alone**.

- Also, there was **no statistically significant difference** in preventing joint damage between **triple therapy** and **MTX in combination** with a biologic (adalimumab, certolizumab, etancercept, or infIximab) or the combination of **MTX and tofacitinib**.

Nonbiologic DMARDs

- **Minocycline** may act as a DMARD through its action as a **matrix metalloproteinase inhibitor** (MMPI).
- **Leflunomide** is the most recent addition to the nonbiologic DMARDs and has **activity similar** to that of **SSZ and MTX**.
- Most of these drugs have been shown to **improve signs and symptoms** (as well as quality of life) and to significantly **retard radiographic** progression of RA.

DMARDs Used for the Treatment of Rheumatoid Arthritis

DRUG	DOSAGE	SERIOUS TOXICITIES	OTHER COMMON SIDE EFFECTS	INITIAL EVALUATION	MONITORING
Hydroxychloroquine	200–400 mg/d orally (≤5 mg/kg)	Irreversible retinal damage Cardiotoxicity Blood dyscrasia	Nausea Diarrhea Headache Rash	Eye examination if >40 years old or prior ocular disease	Optical coherence tomography and visual field testing every 12 months
Sulfasalazine	Initial: 500 mg orally twice daily Maintenance: 1000–1500 mg twice daily	Granulocytopenia Hemolytic anemia (with G6PD deficiency)	Nausea Diarrhea Headache	CBC, LFTs G6PD level	CBC every 2–4 weeks for first 3 months, then every 3 months
Methotrexate	10–25 mg/week orally or SQ Folic acid 1 mg/d to reduce toxicities	Hepatotoxicity Myelosuppression Infection Interstitial pneumonitis Pregnancy category X	Nausea Diarrhea Stomatitis/mouth ulcers Alopecia Fatigue	CBC, LFTs Viral hepatitis panel[a] Chest x-ray	CBC, creatinine, LFTs every 2–3 months
Leflunomide	10–20 mg/d	Hepatotoxicity Myelosuppression Infection Pregnancy category X	Alopecia Diarrhea	CBC, LFTs Viral hepatitis panel[a]	CBC, creatinine, LFTs every 2–3 months

Biologic DMARDs: TNF inhibitors

- The TNF inhibitors that **bind TNF** and thus **prevent its interaction with its receptors** include the following:
- Etanercept
- Infliximab
- Adalimumab
- Certolizumab
- Golimumab

Biologic DMARDs: TNF inhibitors
Precautions and adverse effects

- Biologic agents are **expensive**.
- Consensus statements **do not recommend** their use until at least one nonbiologic DMARD, usually MTX, has been administered without sufficient success.
- In clinical trials, as many as **70% of patients** achieve **significant responses**, but **remissions are not usually observed**

Biologic DMARDs: TNF inhibitors
Precautions and adverse effects

- Adverse effects include :
- generation of **antibodies against** these compounds,
- emergence of antinuclear antibodies (**ANAs**), occasional drug-induced **lupuslike syndromes**, and
- infections (including **tuberculosis**).
- Rarely, **demyelinating disorders** and **bone marrow suppression** occur.
- Immunogenicity, such as the development of **anti-drug antibodies**, has been shown to occur in **adalimumab and infliximab**, potentially leading to decreased drug efficacy.
- **Concomitant use of MTX** may reduce the frequency of anti-drug antibodies.

Biologic DMARDs: TNF inhibitors
Precautions and adverse effects

- Acute and chronic **infections**, **demyelinating disorders**, **class III or IV heart failure**, and recent malignancies are **contraindication**s to the use of TNF inhibitors.
- Thoroughly searching for **latent tuberculosis** using purified protein derivative (**PPD**) testing or an interferon (IFN) gamma release assay (**IGRA**), with or without chest radiography, is recommended before these agents are started.
- Patients taking anti-TNF agents must **avoid live-virus vaccines**.

Biologic DMARDs: TNF inhibitors
Precautions and adverse effects

- Anti-TNF therapy may **double the risk of septic arthritis** in patients with RA, highest in the early months of therapy.
- **joint replacement** surgery was also noted as a **risk factor** for septic arthritis.
- Hepatitis B virus **(HBV) reactivation** (HBsAg and anti-HBc)with detectable occult HBV infection during anti−TNF-a therapy.
- **Antiviral prophylaxis** may effectively **reduce** this reactivation.

- In three Swedish registries that analyzed the cancer risk in 6366 RA patients taking TNF inhibitors, **no increased risk** of **cancer** with these agents was observed

TNF inhibitors vs MTX

- Van Vollenhoven et al reported that in patients with early RA who have **MTX-treatment failure**, the addition of a **TNF antagonist was superior** to the addition of **conventional DMARDs**.

TNF inhibitors
Adalimumab

- According to data from a study of 221 consecutive RA patients, adalimumab blood levels of **5 to 8 µg/mL** have the **greatest effect** on disease activity.
- In the study, adalimumab trough levels **greater than 8 µg/mL** had **no additional beneficial effect** on disease activity.
- **40 mg** adalimumab subcutaneously **every other week**
- Patients treated with concomitant MTX reached recommended **blood levels at lower** adalimumab doses.
- MTX might contribute to **increasing adalimumab blood levels** by **reducing inflammation** and **lowering the number of targets** for adalimumab to bind to.

TNF inhibitors
Certolizumab

- A study by Smolen et al found that certolizumab **plus MTX was more** efficacious than placebo **plus MTX**, rapidly and significantly **improving signs and symptoms** of RA and **physical function** and **inhibiting radiographic progression.**
- In this study, **619 patients** were randomized to receive certolizumab 400 mg at **weeks 0, 2, and 4, followed by 200 mg or 400 mg plus MTX every 2 weeks** or placebo plus MTX every 2 weeks

TNF inhibitors
Golimumab

- Golimumab is a **human anti–TNF-a monoclonal antibody** that inhibits TNF-a bioactivity, thereby modulating immune activity in patients with RA
- golimumab plus MTX is **more efficacious** than MTX alone in **reducing disease signs and symptoms** in MTX-naive patients.
- The most common **adverse events** were "**infections and infestations**," including **upper respiratory tract infection** (>5% of patients), **urinary tract infection**, and **nasopharyngitis.**

Biologic DMARDs: non-TNF agents

- ***Rituximab***
- Treatment with rituximab may **deplete CD20+ B cells**.
- Rituximab is most often used in **combination with MTX**.
- Effective for **reducing signs and symptoms** in adult patients with **moderately to severely** active RA who have had an **inadequate** response to therapy with **one or more TNF inhibitors**.
- The ORBIT study in 295 biological-treatment naive patients with RA found that **initial treatment with rituximab** is noninferior to initial TNF inhibitor treatment.

Biologic DMARDs: non-TNF agents *Anakinra*

- Anakinra is a recombinant nonglycosylated form of the human **IL-1 receptor antagonist** (IL-1ra).
- In clinical trials, a significant response was observed in approximately **40% of patients with RA**.

Biologic DMARDs: non-TNF agents *Abatacept*

- Abatacept is a selective costimulation modulator that **inhibits T-cell activation by binding to CD80 and CD86**, thereby blocking their interaction with CD28.
- CD28 interaction provides a signal needed for the **full T-cell activation** that is implicated in **RA pathogenesis**.
- Maintenance doses of abatacept may be administered as a **monthly** intravenous (IV) infusion or by the patient as a **weekly SC injection**.
- In patients with RA who **treatment failure** with **anti-TNF therapy**, abatacept has been shown to demonstrate consistent **safety and efficacy** that are maintained from 6 months to 5 years of therapy.

Biologic DMARDs: non-TNF agents
Tocilizumab

- Tocilizumab, an **IL-6 receptor inhibitor**, is available as either an IV infusion or SC injection.
- It is indicated for **moderate-to-severe active** RA in adults who have had an **inadequate response to 1 or more TNF-antagonist** therapies.
- It may be used either alone or in combination with MTX or other DMARDs.
- In patients with **inadequate response to TNF inhibitors**, tocilizumab treatment results in **significant, clinically meaningful, rapid, and sustained improvements** in a number of patient-reported outcomes.

Tofacitinib

- **JAK inhibitors** modulate the signaling pathway at the point of JAKs, **preventing the phosphorylation** and activation of STATs.
- These signals maintain the **inflammatory condition** in RA.
- Inhibition of JAKs **reduces production** of and modulates proinflammatory cytokines central to RA.
- The **indication is specific** for patients who have had an **inadequate response to or are intolerant of MTX**.
- Tofacitinib may be given as **monotherapy or in combination** with MTX or other nonbiologic DMARDs.
- It **should not** be used in combination with **biologic DMARDs** or potent immunosuppressive agents (eg, **azathioprine or cyclosporine**).

Tofacitinib

- Tofacitinib is an **oral JAK inhibitor** that was approved by the FDA in November 2012 as **second-line treatment** for **moderate to severe** active RA.
- Tofacitinib has been associated with **reductions in signs and symptoms** of RA and improvement in **physical function**.
- Fleischmann et al demonstrated that ACR criteria for a 20% response were met in **59.8%** of patients receiving **monotherapy** with tofacitinib 5 mg twice daily, compared with **26.7% of patients receiving placebo**.

Tofacitinib

- In another study, in which **717 patients** who received stable **MTX** doses over 12 months were randomized to also receive 5 mg or 10 mg of **tofacitinib** orally twice daily, **adalimumab** 40 mg every 2 weeks, or **placebo** :
- ACR 20% response rates at 6 months were higher among patients receiving **5 mg or 10 mg of tofacitinib (51.5% and 52.6%,** respectively) and among those receiving **adalimumab (47.2%)** than among those receiving **placebo (28.3%).**

- ***Baricitinib***

- The FDA approved a **second JAK inhibitor**, baricitinib (Olumiant), in June **2018 as a second-line treatment** of moderately to severely active RA in adults who have had an **inadequate response to one or more TNF antagonists.**

- ***Upadacitinib***

- Another JAK inhibitor, **upadacitinib** (Xenleta), was approved in August **2019 for moderately to severely active RA** in adults who have had an **inadequate response** or are intolerant to methotrexate.
- It may be used as **monotherapy or in combination** with methotrexate or **other nonbiological DMARDs**.

DRUG	DOSAGE	SERIOUS TOXICITIES	OTHER COMMON SIDE EFFECTS	INITIAL EVALUATION	MONITORING
TNF-α Inhibitors	Infliximab: 3 mg/kg IV at weeks 0, 2, 6, then every 8 weeks. May increase dose up to 10 mg/kg every 4 weeks	↑ Risk bacterial, fungal infections Reactivation of latent TB ↑ Lymphoma risk (controversial) Drug-induced lupus Neurologic deficits	Infusion reaction ↑ LFTs	PPD skin test	LFTs periodically
	Etanercept: 50 mg SQ weekly, or 25 mg SQ biweekly	As above	Injection site reaction	PPD skin test	Monitor for injection site reactions
	Adalimumab: 40 mg SQ every other week	As above	Injection site reaction	PPD skin test	Monitor for injection site reactions
	Golimumab: 50 mg SQ monthly	As above	Injection site reaction	PPD skin test	Monitor for injection site reactions
	Certolizumab: 400 mg SQ weeks 0, 2, 4, then 200 mg every other week	As above	Injection site reaction	PPD skin test	Monitor for injection site reactions

DRUG	DOSAGE	SERIOUS TOXICITIES	OTHER COMMON SIDE EFFECTS	INITIAL EVALUATION	MONITORING
Abatacept	Weight based: <60 kg: 500 mg 60–100 kg: 750 mg >100 kg: 1000 mg IV dose at weeks 0, 2, and 4, and then every 4 weeks OR 125 mg SQ weekly	↑ Risk bacterial, viral infections	Headache Nausea	PPD skin test	Monitor for infusion reactions
Anakinra	100 mg SQ daily	↑ Risk bacterial, viral infections Reactivation of latent TB Neutropenia	Injection site reaction Headache	PPD skin test CBC with differential	CBC every month for 3 months, then every 4 months for 1 year Monitor for injection site reactions
Rituximab	1000 mg IV × 2, days 0 and 14 May repeat course every 24 weeks or more Premedicate with methyl-prednisolone 100 mg to decrease infusion reaction	↑ Risk bacterial, viral infections Infusion reaction Cytopenia Hepatitis B reactivation	Rash Fever	CBC Viral hepatitis panel[a]	CBC at regular intervals
Tocilizumab	4–8 mg/kg 4–8 mg/kg IV monthly OR 162 mg SQ every other week (<100 kg weight) 162 mg SQ every week (≥100 kg weight)	Risk of infection Infusion reaction LFT elevation Dyslipidemia Cytopenias		PPD skin test	CBC and LFTs at regular intervals
Tofacitinib	5 mg orally BID OR 11 mg orally daily	Risk of infection LFT elevation Dyslipidemia Neutropenia	Upper respiratory tract infections Diarrhea Headache Nasopharyngitis	PPD skin test	CBC, LFTs, and lipids at regular intervals

Combination DMARD therapy

- **it is not possible** to predict which patients will not have a treatment response.
- **three strategies** are employed to reduce disease activity as much as possible in patients whose disease does not respond or in those with clinical responses that are regarded as insufficient:
- **Increasing** the dose of medication
- **Switching** to other DMARDs
- **Initiating combination** therapy
- Because patients may **require 2-3 months to achieve a full response** to DMARDs, **decisions** regarding changes in medication are **often delayed** until that time.

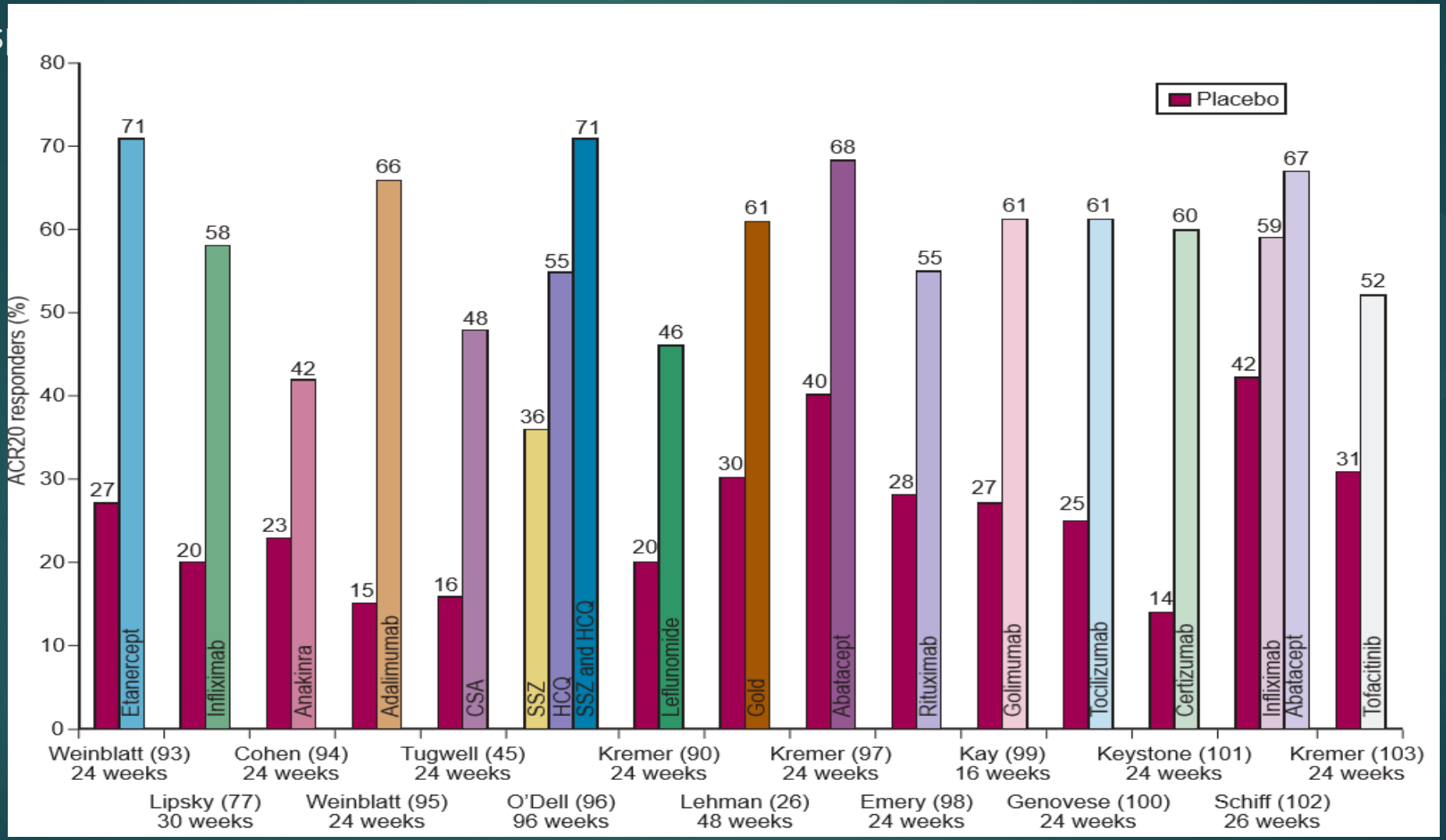
Combination DMARD therapy

- **Several combinations** have proved successful without posing unexpected added risks; most include:
- MTX monothrapy
- **MTX (eg, MTX plus SSZ plus HCQ)**
- **MTX plus leflunomide**
- **MTX plus biologic DMARDs**

Combination DMARD therapy

- MTX combined with **infliximab or rituximab** yields a **better response** than monotherapy does.
- MTX combined with **etanercept** provides a **higher rate of meaningful** clinical response.
- MTX combined with **cyclosporine**, though not a commonly used combination, results in **greater clinical improvement than MTX alone**.
- **Triple therapy** with MTX, SSZ, and HCQ may provide substantially **greater clinical improvement** than **either MTX alone** or **SSZ plus HCQ**.
- The toxicities of these drug combinations are **rarely**
- **liver and bone marrow toxicity** may be increased if **MTX and leflunomide are combined.**

Blinded trials of therapies in patients with active disease despite methotrexate. ACR20, American College of Rheumatology 20% composite improvement; CSA, cyclos



Combination DMARD therapy

- In the investigation, a meta-analysis of 35 studies that included 8733 treated patients with RA and 4664 controls.
- **More than 50%** of patients treated with **biologics** experienced clinically relevant improvement.
- **Etanercept and rituximab** were the **most effective** treatments, both in patients who had **never before taken** antirheumatic drugs and in those who had shown an **inadequate response** to them.

Combination DMARD therapy
Adverse effects

- When used with appropriate **clinical and laboratory control monitoring**, combination therapy with the above agents is usually well **tolerated.**
- Adverse events typically become **rarer** after the **first 2-3 months** of therapy.
- Most adverse events are **reversible** with **cessation** of the drugs or with **reduction** of the doses

Adverse effects DMARD

- The **most important and most common** adverse events relate to :
- **liver and bone marrow toxicity** (MTX, SSZ, leflunomide, azathioprine, gold compounds, and D-penicillamine),
- **Renal toxicity** (cyclosporine, parenteral gold salts, and D-penicillamine),
- **pneumonitis** (MTX)
- **allergic skin reactions** (gold compounds and SSZ),
- **autoimmunity** (D-penicillamine, SSZ, and minocycline)
- **infections** (azathioprine and cyclosporine).
- **Antimalarial agents** may cause **ocular toxicity**. (ophthalmologic screening)

Complications of DMARD treatment

- DMARDs, with combination therapy, including **biologic agents such as TNF antagonists**, may present with serious **infections, malignancies, or both**.

TNF precautions and mortality

- Patients taking anti-TNF agents must **avoid live-virus vaccines** (eg, measles-mumps-rubella [**MMR**], **HZV**, varicella-zoster virus [**VZV**], and bacillus Calmette-Guérin [**BCG**] vaccines) .
- The results from another study confirmed that the **risk of serious infection and malignancy** is **not increased** in patients **receiving anti-TNF therapy** when the patients have **early RA** and have not been previously treated with MTX or other DMARDs.
- In a systematic review and meta-analysis showed that these agents did **not increase the risk of malignancy**, particularly **lymphoma**; however, they did appear to **increase the risk of skin cancer**, including **melanoma**.

Corticosteroids

- Corticosteroids are potent **anti-inflammatory drugs bridge the time until treatment with DMARDs** is effective.
- These agents are **effective adjuncts** to DMARD or NSAID therapy.
- Timely **dose reductions and cessation** are important because of the **adverse effects** associated with long-term steroid use.
- Corticosteroids can be administered by oral, IV, or intra-articular routes.
- ***Adverse effects***
- **One study** found that the use of corticosteroids was associated with **heart failure** in patients with RA, independent of cardiovascular risk factors and coronary heart disease (CHD).
- Those patients who currently used MTX showed a **lower risk of heart failure.**

Corticosteroids *Adverse effects*

- The risk of adverse effects of a glucocorticoid is dependent on the disease, comorbidities, patient, dose, and duration of therapy.

System	Adverse Effect
Skeletal	Osteoporosis, osteonecrosis, myopathy
Gastrointestinal	Peptic ulcer disease (especially in combination with NSAIDs), pancreatitis, fatty liver
Immunologic	Predisposition to infections, suppressed delayed hypersensitivity (tuberculin skin test)
Cardiovascular	Fluid retention, hypertension, accelerated arteriosclerosis, arrhythmias
Ocular	Glaucoma, cataract
Cutaneous	Skin atrophy, striae, ecchymoses, impaired wound healing, acne, buffalo hump, hirsutism
Endocrine	Cushingoid appearance, diabetes mellitus, changes in lipid metabolism, enhanced appetite and weight gain, electrolyte abnormalities, HPA axis suppression, suppression of gonadal hormones
Behavioral	Insomnia, psychosis, emotional instability, cognitive effects

Nonsteroidal anti-inflammatory drugs

- NSAIDs interfere with **prostaglandin synthesis** through **inhibition of the enzyme cyclooxygenase** (COX), thus **reducing swelling and pain**.
- However, they do **not retard joint destruction** and thus are **not sufficient to treat RA when used alone**.
- Like corticosteroids, NSAIDs can be **reduced in dose or discontinued with successful DMARD therapy**.
- **Commonly used NSAIDs** include ibuprofen, naproxen, ketoprofen, piroxicam, and diclofenac.

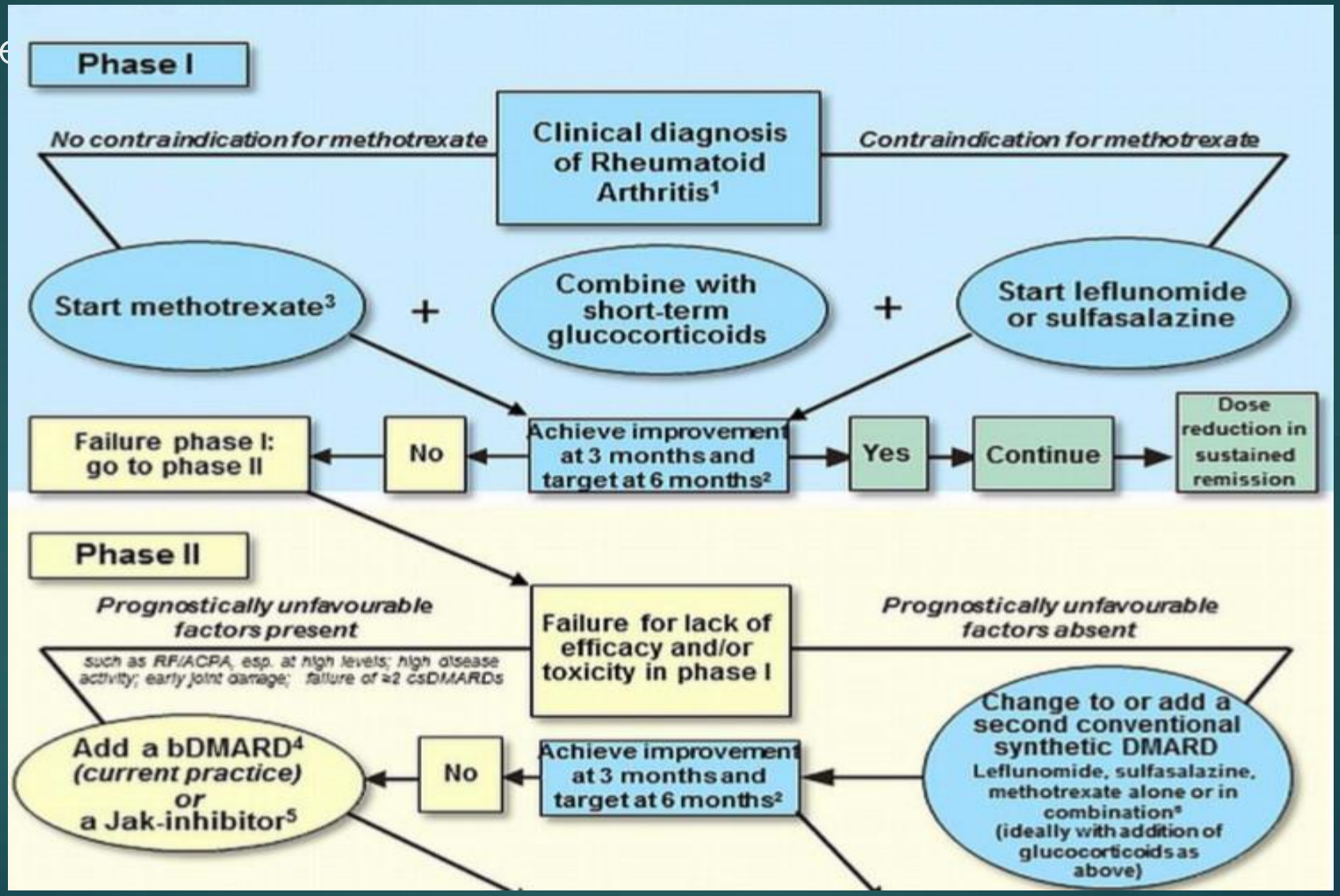
Nonsteroidal anti-inflammatory drugs
Adverse effects

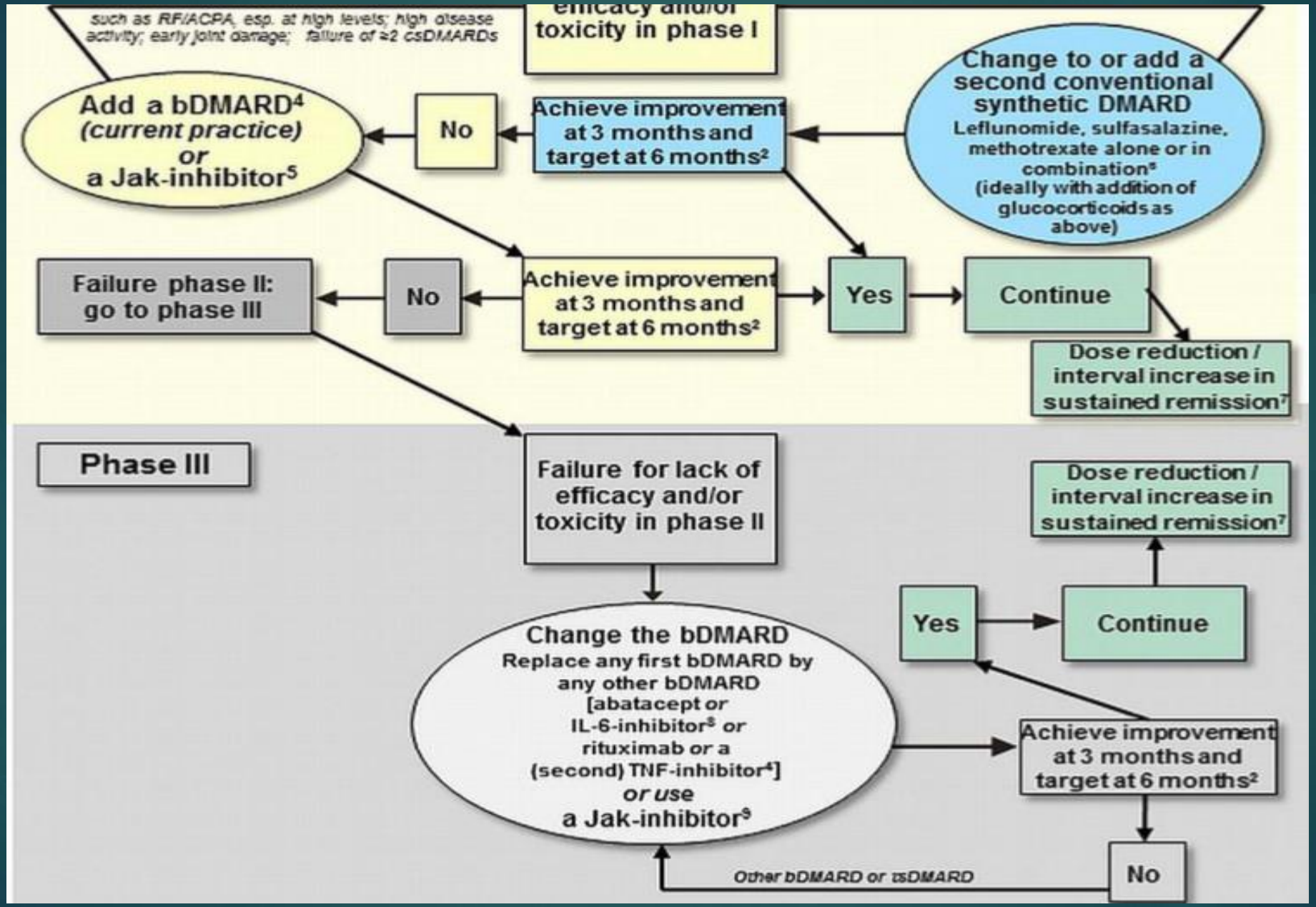
- Coxibs, with their **selectivity for COX-2**, **reduced gastrointestinal** (GI) toxicity, the **major adverse event** related to the use of **nonselective COX inhibitors (ie, NSAIDs)**.
- Other adverse effects, such as **water retention**, **hypertension**, and **abnormal transaminase levels**, are observed with **both** nonselective COX inhibitors and selective COX-2 inhibitors.
- comparing celecoxib with placebo found that the risk of **cardiovascular death, myocardial infarction, stroke, heart failure, or thromboembolic** events **increased** after celecoxib treatment.

Analgesics

- Acetaminophen, tramadol, codeine, opiates, and various other analgesic medications can also be used to **reduce pain**.
- These agents **do not affect** swelling or joint destruction.

Algorithm based on European League Against Rheumatism (EULAR) recomme




such as RF/ACPA, esp. at high levels; high disease activity; early joint damage; failure of ≥2 csDMARDs
toxicity in phase I
Change to or add a second conventional synthetic DMARD
Leflunomide, sulfasalazine, methotrexate alone or in combination[3]
(ideally with addition of glucocorticoids as above)
Add a bDMARD[4]
(current practice)
or
a Jak-inhibitor[5]
No
Achieve improvement at 3 months and target at 6 months[2]
Failure phase II: go to phase III
No
Achieve improvement at 3 months and target at 6 months[2]
Yes
Continue
Dose reduction / interval increase in sustained remission[7]
Phase III
Failure for lack of efficacy and/or toxicity in phase II
Dose reduction / interval increase in sustained remission[7]
Yes
Continue
Change the bDMARD
Replace any first bDMARD by any other bDMARD
[abatacept or IL-6-inhibitor[6] or rituximab or a (second) TNF-inhibitor[4]]
or use
a Jak-inhibitor[6]
Achieve improvement at 3 months and target at 6 months[2]
Other bDMARD or tsDMARD
No

Experimental therapies

- It remains active in many patients whose conditions partially or completely fail to respond to DMARDs.
- Therefore, the vigorous search for new therapeutic agents continues.
- Several **new CD20 B-cell–targeted biologic agents** are under investigation, including atacicept, AMG 623, B3-FCc, Br3-Fc, belimumab, epratuzumab, ofatumumab, ocrelizumab, and TRU-015.
- Small molecules directed at enzymes involved in signal transduction of TNF and other proinflammatory cytokines are effective in treating RA.
- A phase II study reported that in comparison with placebo, **fostamatinib**, an **inhibitor of spleen tyrosine kinase (Syk)**, reduced disease activity in RA patients who did not have a response to MTX therapy. [148] Further investigation is required to determine the safety and efficacy of this agent in RA patients.
- **Inhibition of matrix metalloproteinases** (MMPs), though initially unsuccessful, could prove to be efficacious, as could inhibition of osteoclast activation.
- **Apheresis procedures** are also being investigated.
- High-dose immunosuppression combined with **autologous stem cell transplantation** has been used in study protocols for patients whose conditions are resistant to other therapies.

موفق باشید