Rheumatoid Arthritis

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Objectives

1. Recognize the clinical presentation of rheumatoid arthritis (RA).
2. Describe the mechanisms of action and clinical uses of available biologic and non-biologic disease-modifying anti-rheumatic drugs (DMARDs) for rheumatoid arthritis.
3. Synthesize a safety and efficacy plan for any given therapy.

RA Guidelines

- 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis

- EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update

RA Clinical Background

- Epidemiology
  - Annual incidence 40 per 100,000
  - Female > Male
  - Any age (initial presentation 30-50 years old)
- Etiology
  - Genetic predisposition and environmental factors
- Pathophysiology
  - Overactivation of T cells leaving to overstimulation of B cells which in turn produce antibodies
  - Immune cell migration and cytokine stimulation lead to hypertrophy, inflammation, and destruction

Rheumatology (Oxford). 2000 Jan; 39(1):28-33.

Presentation

- Joint stiffness upon awakening
- Swelling in specific fingers or wrist joints (with/without pain)
- Small joint inflammation ≥ 6 weeks duration
- Swelling in soft tissues around the joints
- Symmetrical pattern of affected joints

Presentation

- Fatigue, depression, fevers, anemia, general malaise
- Vasculitis
- Pleural effusions, pulmonary fibrosis
- Sjogren's Syndrome
- Pericarditis, conduction abnormalities, myocarditis
- Felty's Syndrome
- Symptoms generally last for years and get progressively worse

ACR/EULAR RA Classification Criteria

Criteria	Score
Joint Involvement (at least one joint not explained by another disease) • 2-10 large joints • 1-3 small joints (+/- large joint) • 4-10 small joints (+/- large joint) • >10 joints (at least one small joint)	 1 2 3 5
Low-positive RF or anti-CP antibody	2
High-positive RF or anti-CP antibody	3
High ESR or CRP	1
Duration of symptoms $\geq$ 6 weeks	1

Six or more criteria must be met (one must be serology)

Ann Rheum Dis. 2010;69:1589-95

Keys to RA Diagnosis

- History and physical
- Blood work
- Imaging
- Important to recognize signs and symptoms of RA and recommend referral if they are present

Goals of Therapy

- Achieve remission or low disease activity as quickly as possible
  - Relieve pain, inflammation, and stiffness
- Maintain or improve function for activities of daily living
  - Prevent or limit work disability
  - Maintain or maximize independence
- Maximize quality of life
- Minimize risk of therapy

Non-Pharmacologic Treatment

- Physical Therapy
- Occupational Therapy
- Physical Conditioning
- Pain Coping Skills
- Disease State Education
- Tobacco Cessation
- Mental Health
- Nutrition
- Podiatry

Pharmacologic Treatment

NSAIDs
Ibuprofen
Naproxen
Others

COX-2 inhibitor
Celecoxib

Corticosteroids
Prednisone
Triamcinolone

Analgesics
Acetaminophen
Tramadol
Opioids

Traditional DMARDs (csDMARDs)
Methotrexate
Leflunomide
Sulfasalazine
Hydroxychloroquine

Biologics (bDMARDs) (TNF, non-TNF)
Adalimumab
Etanercept
Infliximab
Golimumab
Certolizumab
Rituximab
Abatacept
Tocilizumab
Sarilumab

Biosimilars
Infliximab-dyyb
Infliximab-abda
Infliximab-axxq

Oral Synthetic Small Molecule (OSSM)(tsDMARDs)
Tofacitinib
Baricitinib
Upadacitinib

DMARD = Disease Modifying Anti-Rheumatic Drug

Nonsteroidal Anti-Inflammatory Drugs

- Do **NOT** alter disease course
- Should not be used as monotherapy
- Doses may vary between patients
- Gastric side effects common
  - Choose another NSAID
  - Gastroprotection with PPI
- May cause renal failure in pre-disposed patients
  - Elderly
  - Pre-existing renal disease
- Cardiovascular risk

NSAID = nonsteroidal anti-inflammatory drug, PPI = proton pump inhibitor

Corticosteroids

- Some evidence for disease modifying activity
- Useful when initiating DMARD as effects are immediate
- Taper and stop or use lowest possible dose

Triamcinolone acetate Dosing	
IM	60mg every 6 weeks with 20-100mg IM PRN
IA	Large joints: 15-40mg Small joints: 2.5-10mg 2-3x/year PRN Consider use of local anesthetic

Monitoring
Blood pressure
Glucose readings/A1c
Cataracts
Quality of sleep/Mood
Osteoporosis risk

IM = intramuscular, IA = intra-articular, PRN = as needed

Traditional Disease-Modifying Antirheumatic Drugs (csDMARDS)

Methotrexate (Trexall®)

Mechanism of Action	folic acid antagonist
Dosing	7.5-25mg PO every 7 days *Consider IM or subcut administration if >15mg/week *Avoid in patients with CrCl <30 min/m^2
Side Effects	GI upset, Rash
Lab Monitoring	CBC, SCr, liver transaminases < 3 months: every 2-4 weeks 3-6 months: every 8-12 weeks > 6 months: every 12 weeks Albumin: periodically
Toxicity	Myelosuppression, Hepatotoxicity, Cirrhosis, Pulmonary toxicity
Counseling Pearls	• Emphasize importance of weekly dosing • Onset of action usually weeks to months • Avoid alcohol • Supplement with folic acid 1mg daily
Pregnancy Category	X (teratogenic)

PO = by mouth, IM = intramuscular, subcut = subcutaneous, CBC = complete blood count, SCr = serum creatinine

Leflunomide (Arava®)

Mechanism of Action	inhibits mitochondrial enzyme dihydroorotate dehydrogenase
Dosing	10-20mg PO daily *70-100mg loading dose optional *consider every other day dosing or dose reduction if experiencing side effects
Side Effects	GI upset (diarrhea), Alopecia
Lab Monitoring	CBC, SCr, liver transaminases < 3 months: every 2-4 weeks 3-6 months: every 8-12 weeks > 6 months: every 12 weeks Albumin: periodically
Toxicity	Hepatotoxicity, Cirrhosis
Counseling Pearls	• Cholestyramine (8 gm three times daily for 11 days) is recommended to wash out drug prior to pregnancy or in the case of severe toxicity given enterohepatic circulation results in very long elimination half life Avoid alcohol
Pregnancy Category	X (teratogenic)

PO = by mouth, CBC = complete blood count, SCr = serum creatinine

Sulfasalazine (Azulfidine®)

Mechanism of Action	largely unknown; cleaved in the intestine to sulfapyridine and 5-aminosalicylic acid (active metabolite)
Dosing	500mg PO BID and titrate to 1000-1500mg BID *titrate to reduce GI side effects *dose with food *standard and enteric-coated formulations available
Side Effects	GI upset (diarrhea), Rash
Lab Monitoring	CBC, SCr, liver transaminases < 3 months: every 2-4 weeks 3-6 months: every 8-12 weeks > 6 months: every 12 weeks Albumin: periodically
Toxicity	Myelosuppression
Counseling Pearls	• Avoid in sulfa allergy • Monitor for signs/symptoms of an allergic reaction • May turn urine yellow-orange in color
Pregnancy Category	B

PO = by mouth, BID = twice daily, CBC = complete blood count, SCr = serum creatinine

Hydroxychloroquine (Plaquenil®)

Mechanism of Action	Antimalarial with anti-inflammatory properties
Dosing	200mg PO BID
Side Effects	GI upset, myopathy, headache
Lab Monitoring	None
Toxicity	Eye toxicity (possibly even blindness), Rash *Eye exam with peripheral visual field test every 12 months
Counseling Pearls	Generally well-tolerated
Pregnancy Category	B

PO = by mouth, BID = twice daily

Biologics (bDMARDs)

Biologics

Tumor Necrosis Factor Inhibitors	Non-Tumor Necrosis Factor Inhibitors
"Anti-TNFα agents, TNF inhibitors, TNFi"	"non-TNF inhibitors, non-TNFi"
Certolizumab **A**dalimumab **I**nfliximab **G**olimumab **E**tanercept Bind to the cytokine TNF and inhibit its interaction with the TNF receptors	Abatacept T-cell co-stimulation modulator (binds to CD80/86) Rituximab monoclonal antibody to CD20 surface marker positive B cells Tocilizumab IL-6 receptor antibody Sarilumab IL-6 receptor antibody

Tumor Necrosis Factor Inhibitors

Often called Anti-TNFα agents or TNF inhibitors or TNFi

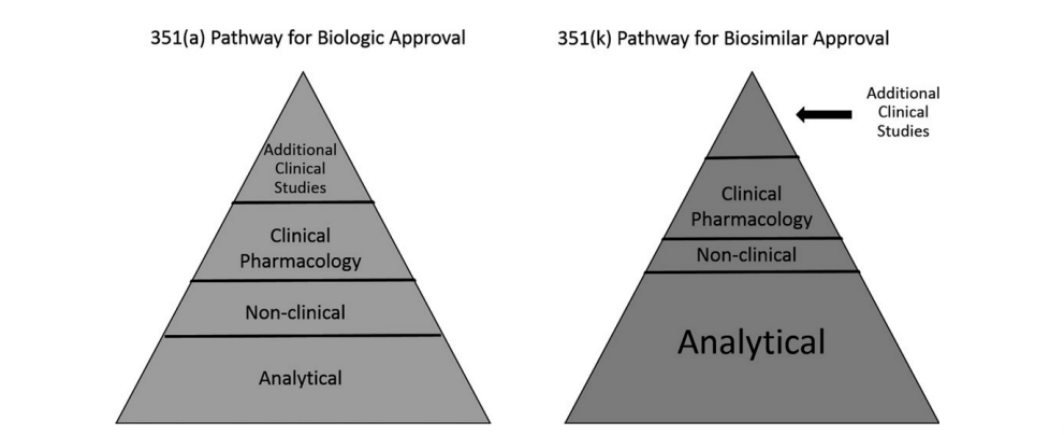
Monoclonal Antibody	Dosing
Adalimumab (Humira®)	40mg **subcut** every 2 weeks
Golimumab (Simponi®)	50mg **subcut** every month
Infliximab (Remicade®)	3mg/kg **IV** at Week 0, Week 2, Week 6 then 3mg/kg every 8 weeks, may increase up to 10mg/kg dose or increase frequency to every 4 weeks *Give with methotrexate
Certolizumab pegol (Cimzia®)	400mg **subcut** at 0, 2, 4 weeks then 200mg **subcut** every 2 weeks *or* 400mg **subcut** every 4 weeks

Fusion Protein	Dosing
Etanercept (Enbrel®)	50mg **subcut** once weekly

Subcut = subcutaneous, IV = intravenous

Biosimilars

- Use of the reference biologic to reverse engineer the biosimilar product
- Companies do not have access to proprietary manufacturing procedures of the original biologic



- Many approved but only three are commercially available in the US
  - Infliximab-dyyb (Inflectra®)
  - Infliximab-abda (Renflexis™)
  - Infliximab-axxq (Avsola™)
- Therapeutic use is often dictated by formulary or insurance plans

Arthritis & Rheumatology. 2018; 1–11.

Biosimilars

Therapy	Dosing
Infliximab-dyyb (Inflectra®)	3mg/kg **IV** at Week 0, Week 2, Week 6 then 3mg/kg every 8 weeks *May increase up to 10mg/kg maintenance dose *May increase frequency to every 4 weeks *Premedicate with IV corticosteroid, APAP, antihistamine *Prescribed with MTX
Infliximab-abda (Renflexis™)	3mg/kg **IV** at Week 0, Week 2, Week 6 then 3mg/kg every 8 weeks *May increase up to 10mg/kg maintenance dose *May increase frequency to every 4 weeks *Premedicate with IV corticosteroid, APAP, antihistamine *Prescribed with MTX
Infliximab-axxq (Avsola™)	3mg/kg **IV** at Week 0, Week 2, Week 6 then 3mg/kg every 8 weeks *May increase up to 10mg/kg maintenance dose *May increase frequency to every 4 weeks *Premedicate with IV corticosteroid, APAP, antihistamine *Prescribed with MTX

IV = intravenous, APAP = acetaminophen, MTX = methotrexate

Non-Tumor Necrosis Factor Inhibitors

Therapy	Dosing
Abatacept (Orencia®)	500mg (<60kg), 750mg (60-100kg), 1g (>100kg) **IV** at Week 0, Week 2 & then every 4 weeks OR weight-based **IV** loading dose followed by 125mg **subcut** weekly
Rituximab (Rituxan®)	1g **IV** x 2 doses 2 weeks apart *Premedicate with IV corticosteroid, acetaminophen, antihistamine *Prescribed with MTX

Subcut = subcutaneous, IV = intravenous, MTX = methotrexate

Non-Tumor Necrosis Factor Inhibitors

Therapy	Dosing
Tocilizumab (Actemra®)	4mg/kg **IV** every 4 weeks may increase to 8mg/kg if needed (NMT 800mg/dose) OR <100 kg: 162 mg **subcut** every 2 weeks ≥100 kg: 162 mg **subcut** weekly
Sarilumab (Kevzara®)	200mg **subcut** every 2 weeks

Tocilizumab and sarilumab require routine lab monitoring

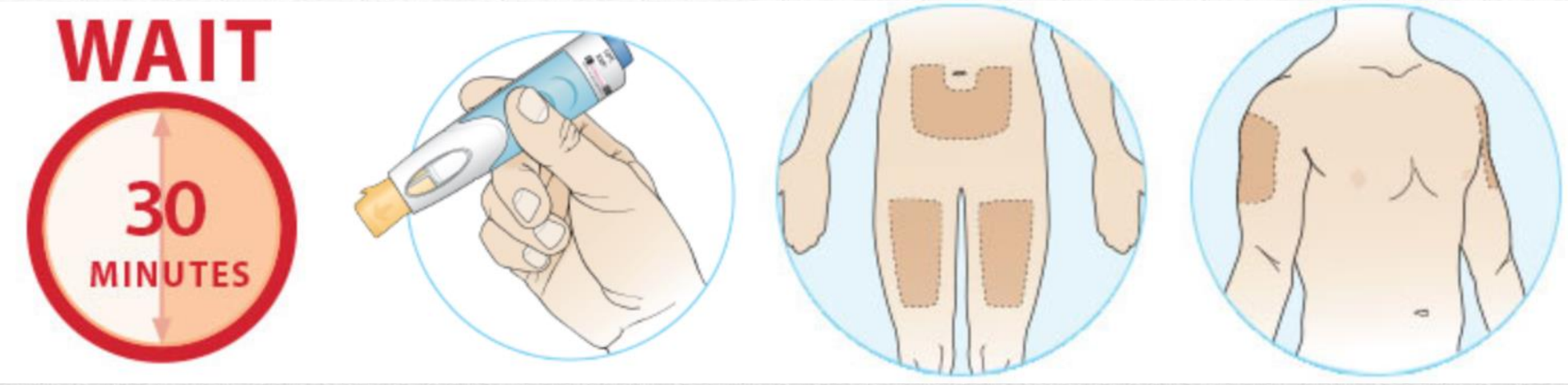
Monitoring Frequency	CBC	AST/ALT, Alk Phos, T.Bili	Lipid profile
Baseline	X	X	X
After 4-8 weeks on therapy	X	X *for 6 months	X
Every 3 months	X	X	

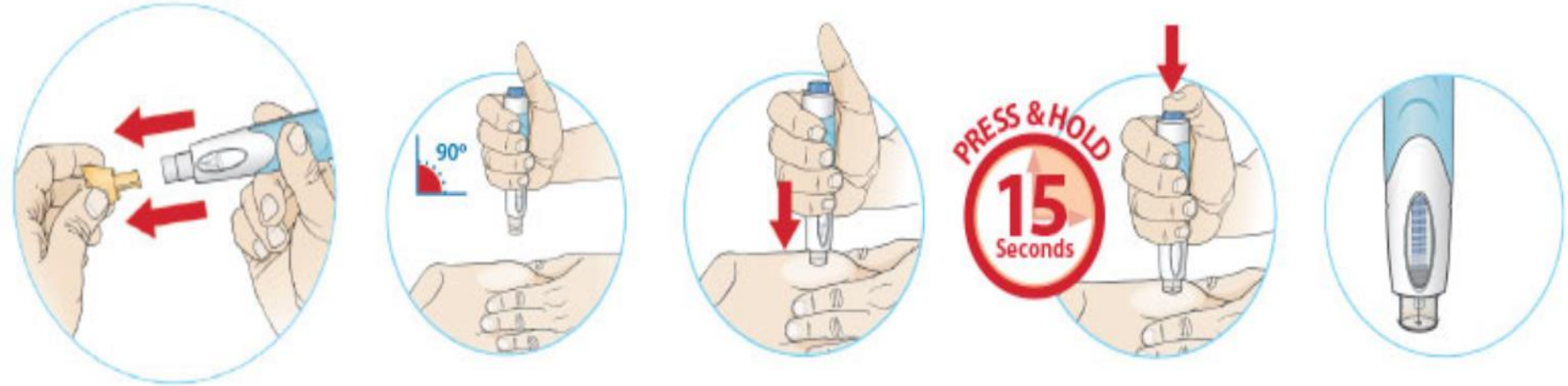
SC = subcutaneous, IV = intravenous

Biologic Considerations and Pearls

- Consider combination with methotrexate
- Do not combine a biologic with another biologic
- Most are pregnancy category B, C, or unknown
- Common side effects include headache, GI upset (N/V/D), upper respiratory infections, injection site reactions, rash
- Increased risk of malignancy (lymphoma)
- Patient education required for administration technique, disposal for subcutaneous therapy or peri-infusion therapy and scheduling

Biologic Administration





Sample patient education video: https://www.humira.com/humira-complete/injection

Biologic Considerations and Pearls

- Increased infection risk
  - Do not use if patient has active/chronic infection
  - Stop immediately if an infection develops
  - Restart once back to baseline and after antibiotic therapy is completed
  - Assess at every visit or when dispensing medication
- Baseline Tuberculosis testing
  - Initial tuberculin skin test or interferon-release assay blood test
  - Treat latent or active infection prior to biologic initiation
  - Patients with risk factors for future or ongoing TB exposure should have annual screening
- Baseline Hepatitis B and Hepatitis C testing

Arthritis & Rheumatology. 2016; 68:1–26.

Biologic Management with COVID-19

Symptomology	COVID-19 Exposure	COVID-19 Test	Therapy Plan
Asymptomatic	No	No	Continue
	Yes	No	Resume after 2 weeks of no symptoms **glucocorticoids may be continued
		Yes-Negative	Resume immediately
		Yes-Positive	Resume 10-17 after positive test **glucocorticoids may be continued

Symptomology	Symptom Severity	Therapy Plan
Symptomatic and confirmed COVID positive test	Uncomplicated	Resume after 7-14 days of symptom resolution
	Severe	Individualized plan

Arthritis Rheumatol. 2020;10.1002/art.41437.
Ann Rheum Dis. 2020; 79:851-858.

Biologic Considerations

- Immunizations - Prior to treatment
  - No restrictions
  - Preferred time to vaccinate
  - May receive multiple immunizations at one time
- Immunizations - During therapy as needed
  - No restrictions with killed or recombinant vaccines*
    - Pneumococcals, Influenza (IM), Hepatitis B, HPV
    - Herpes Recombinant (Shingrix)**
    - COVID-19***
  - Live-attenuated vaccines are not recommended*
    - Influenza (nasal), Yellow Fever, Tuberculosis*

*= Not an all inclusive list ** = Exception to the rule *** = May require a short therapy hold

Oral Synthetic Small Molecule (tsDMARD)

Janus Kinase (JAK) Inhibitors

	Tofacitinib (Xeljanz®)	**Baricitinib (Olumiant®)**	**Upadacitinib (Rinvoq®)**
Dosing	5mg PO BID (IR) 11mg PO daily (XR) Adjustment: 5mg PO daily (IR/XR) *moderate-severe renal impairment *liver disease *CYP3A4 or CYP2C19 inhibitors	2mg PO BID Do not use with eGFR <60 ml/min/m^2	15mg PO daily CYP3A4 and CYP2D6 interactions but no dose adjustments needed
Side Effects	Increased risk of infection, Headache, Diarrhea, Hypertension	Increased risk of infection (upper respiratory tract), Nausea	Increased risk of infection, Nausea, Cough

PO = by mouth

Janus Kinase (JAK) Inhibitors

	Tofacitinib (Xeljanz®)	Baricitinib (Olumiant®)	Upadacitinib (Rinvoq®)
Labs	CBC*, AST/ALT**, Lipids***		CBC*, AST/ALT**
Toxicity	Hepatotoxicity, Malignancy, Lymphoproliferative disorders, Thrombosis, GI perforations		
Counseling Pearls	• Same immunization considerations as biologics • Same infection mitigation strategies as biologics • Not recommended for use with biologics or other JAK inhibitors • Requires baseline TB testing prior to initiation		
Pregnancy Category	C	Limited information	

*Baseline, after 4-8 weeks, every 3 months, **Baseline, ***After 4-8 weeks, periodically

Pharmacologic Treatment

NSAIDs
Ibuprofen
Naproxen
Others

COX-2 inhibitor
Celecoxib

Corticosteroids
Prednisone
Triamcinolone

Analgesics
Acetaminophen
Tramadol
Opioids

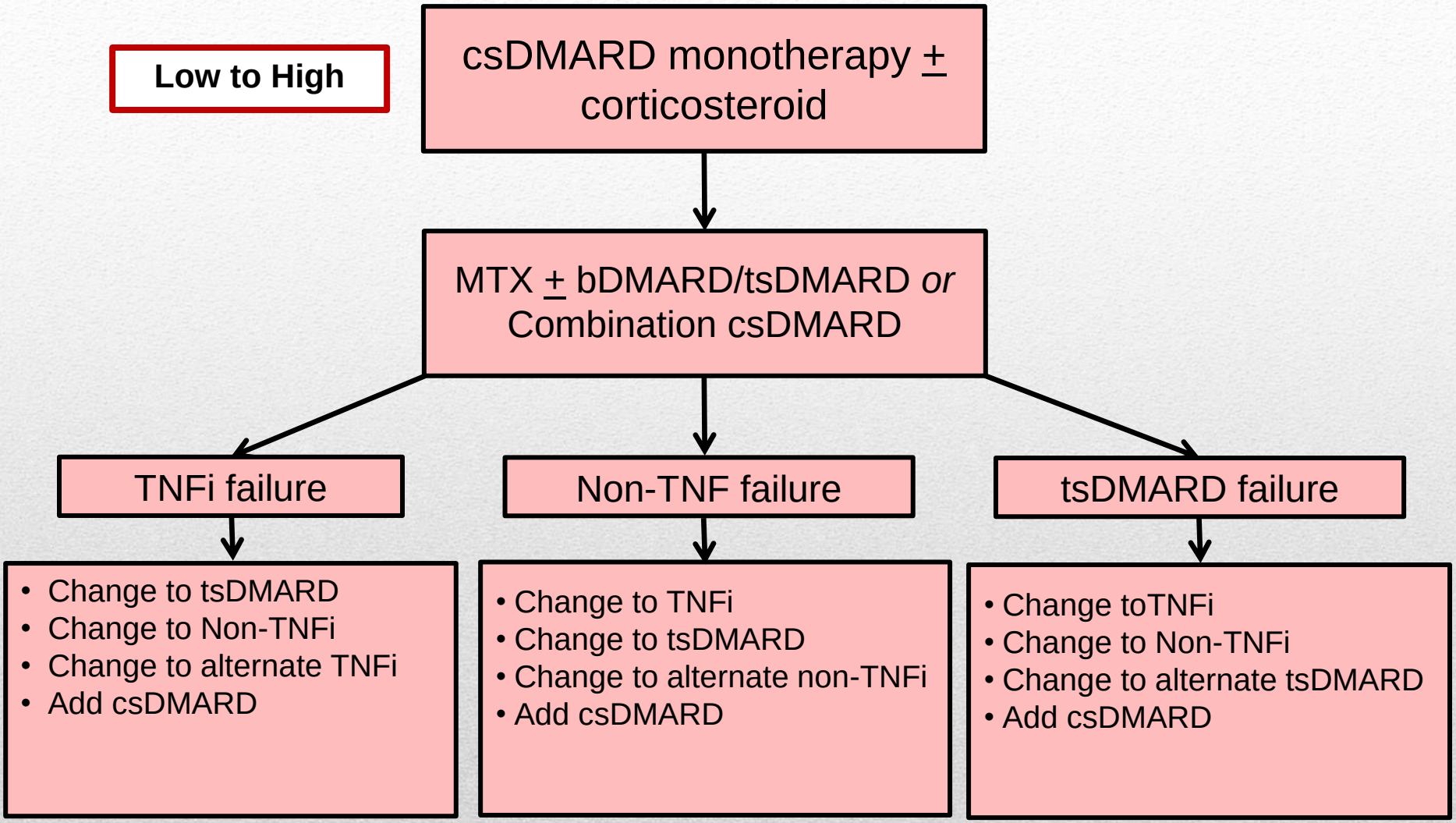
Traditional DMARDs (csDMARDs)
Methotrexate
Leflunomide
Sulfasalazine
Hydroxychloroquine

Biologics (bDMARDs) (TNF, non-TNF)
Adalimumab
Etanercept
Infliximab
Golimumab
Certolizumab
Rituximab
Abatacept
Tocilizumab
Sarilumab

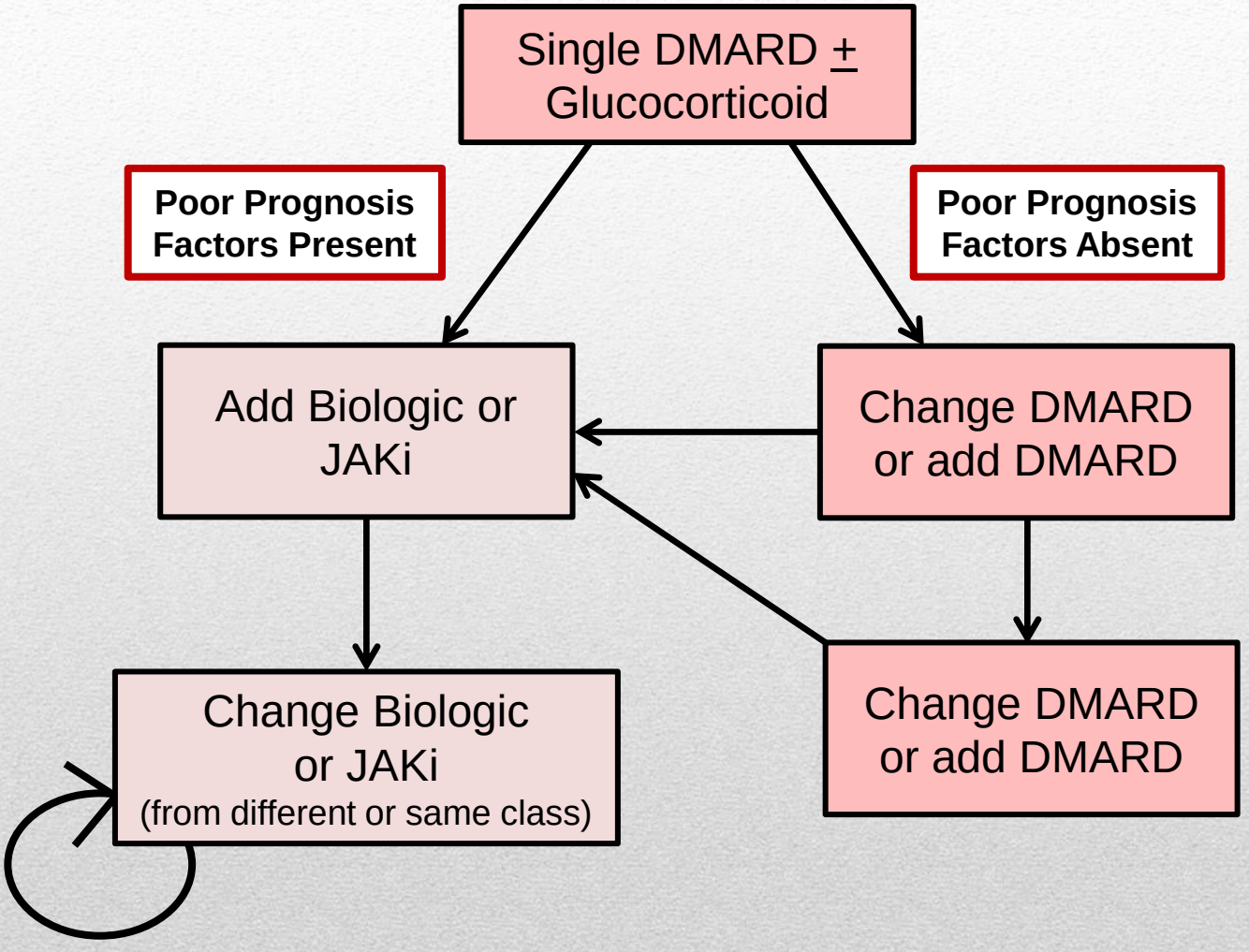
Biosimilars
Infliximab-dyyb
Infliximab-abda
Infliximab-axxq

Oral Synthetic Small Molecule (OSSM)(tsDMARDs)
Tofacitinib
Baricitinib
Upadacitinib

DMARD = Disease Modifying Anti-Rheumatic Drug



Arthritis Care & Research. 2021; 73(7):924–939.



Ann Rheum Dis. 2020; 79:685-699.

Therapy Considerations

- Disease activity
- Allergies
- Comorbidities
- Medication trials
- Insurance
- Administration preference
- Adherence
- Pregnancy
- Non-pharmacologic treatment

Therapy Considerations

High-Risk Conditions	Recommended
Hepatitis C and not receiving antiviral treatment	csDMARDs (SSZ, HCQ) **>** bDMARDs
Previously treated or untreated skin cancer	csDMARDs **>** bDMARDs or ts DMARDs
Previously treated lymphoproliferative disorder	Rituximab **>** Other DMARDs
Heart failure (stable NYHA Class I or II)	Combination csDMARD **or** non-TNF biologic **or** tofacitinib **>** TNFi
Heart failure (worsening NYHA Class I or II or any NYHA Class III or IV)	Combination csDMARD **or** non-TNF biologic **or** tofacitinib
Previous Serious Infection	Combination csDMARD **>** MTX + bDMARD Combination csDMARD **>** MTX + tsDMARD
COPD	Other DMARDs > Abatacept

Arthritis & Rheumatology. 2016; 68:1–26.
Arthritis Care & Research. 2021; 73(7):924–939.

Duration of Therapy

- Lifelong therapy is generally indicated
- Patients may wish to minimize overall exposure to therapy
- Must maintain a therapeutic dose of at least one agent
- Therapy taper options should only be considered if low disease activity present or symptoms have been in remission for ≥ 6 months
- Therapy taper options
  - Dose reduction: decrease dose or increase dosing interval
  - Gradual discontinuation = decrease dose with subsequent goal of stopping therapy

Arthritis Care & Research. 2021; 73(7):924–939.

Pipeline Therapies

- JAK inhibitors (Peficitinib; Tofacitinib as 1st line therapy, and others)
- IL-6 inhibitors (Sirukumab)
- P38-alpha MAPK inhibitor
- Anti-TNF-alpha Nanobody (ozoralizumab)
- Iberiotoxin
- Apremilast for RA
- Ticagrelor for MTX-resistant RA
- Meditation and Neural Targets in RA
- Mindfulness Based Stress Reduction in Rheumatic Diseases
- Host Microbiome in RA

NIH: U.S. National Library of Medicine. Clinicaltrials.gov. Accessed 22 Nov. 2021.

Keys Takeaways

- Rheumatoid arthritis is not only disabling but increases mortality
- Begin therapy with DMARDs as early as possible in order to impact survival
- Treatment should be managed by a rheumatology specialist and specialty team
- Treatment choice is dependent on a variety of factors
- Non-pharmacologic recommendations should be incorporated into treatment plan
- Monitor for toxicity and therapeutic benefit

Supplemental Material

- **Read**
  - DiPiro Pharmacotherapy Chapter: Gruber S, Lezcano B, Hylland S. Rheumatoid Arthritis. In: DiPiro JT, Yee GC, Posey L, Haines ST, Nolin TD, Ellingrod V. eds. *Pharmacotherapy: A Pathophysiologic Approach, 11e*. McGraw Hill; 2020. https://accesspharmacy.mhmedical.com/content.aspx?bookid=2577&sectionid=238237911
  - ACR Guidelines: https://www.rheumatology.org/Portals/0/Files/2021-ACR-Guideline-for-Treatment-Rheumatoid-Arthritis-Early-View.pdf
  - EULAR Guidelines: https://ard.bmj.com/content/79/6/685
- **Listen**
  - Podcasts on role of nutrition in arthritis management: https://www.arthritis.org/liveyes/podcast/nutrition
  - Podcasts about various topics on rheumatologic management: https://www.rheumatology.org/Learning-Center/Publications-Communications/Podcast
- **Watch**
  - Difference between RA and OA: https://www.webmd.com/arthritis/video/arthritis-types
  - Presentation of RA: https://mdmercy.com/centers-of-excellence/additional-centers/rheumatology/conditions-we-treat/rheumatoid-arthritis

Rheumatoid Arthritis

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