Rheumatoid Arthritis

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Introduction

What is rheumatoid arthritis?

How is it different than “arthritis”?

What are the symptoms?

How is it diagnosed?

Options for treatment?

Rheumatoid Arthritis

Chronic, systemic inflammatory disease that primarily affects the joints

Arthritis vs Rheumatoid Arthritis

Arthritis

- Associated with aging, injury, obesity
- Affects middle aged to older people
- Symptoms worse with use
- Very common
- Often involves weight bearing joints such as back, neck, knees, hips

Rheumatoid Arthritis

- Autoimmune
- Affects young, middle aged and older people
- Symptoms typically worst in the morning or after inactivity
- 0.5% to 1% of the population
- Predominately small joint involvement

Rheumatoid Arthritis

Estimate - 1.5 million people in U.S.[1]

Peak incidence between 50 and 75 years old

Lifetime risk 3.6% for women, 1.7% for men[2]

Rheumatoid Arthritis

Female to male ratio of 2-3:1

Occurs among all races, ethnicities

Etiology

Cause remains unknown

Abnormal immune response which leads to chronic inflammation in the joints

Etiology

Genetics

Environmental

Hormonal

Genetics

Twins and siblings of RA patients have greater risk for RA[4,5]

Parents or siblings with RA increase risk of development of RA[6]

HLADR4, PTPN22 genes

Environmental

Cigarette Smoking[7,8,9]

Obesity[8]

Infection –bacterial and viral[10,11,12,13,14]

Microbiome[15]

Silica[16]

Hormones

Women > men

Often improves during pregnancy

Clinical Features

Joint pain and swelling

Fatigue

Morning Stiffness

Clinical Features

Rheumatoid nodules

Pleuritis / pericarditis

Episcleritis / scleritis

Interstitial lung disease

Coronary artery disease

Episcleritis

Clinical Features

Secondary Sjogren's syndrome

Felty's syndrome

Vasculitis

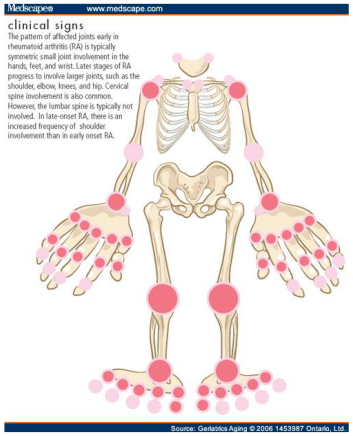
Clinical Features

Hands - MCP, PIP joints

Wrists, shoulders > elbows

Feet - MTP joints, PIP joints

Ankles, Knees



Clinical Features

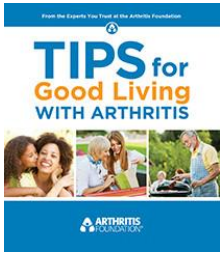
Jaw (TMJ)

Neck

Sternoclavicular, acromioclavicular

DIP joints (hands)

Hips



Clinical Features

Variability in disease

Classic pattern - symmetrical, multiple joints

Single or few joints

Fluctuating symptoms or consistent symptoms

Diagnosis

History, physical exam, and labs

X-rays can help confirm

ACR / EULAR has published diagnostic criteria for RA[17]

RA if score of 6 or greater

Joint involvement (0–5)	
1 med/large joint	0
2–10 med/large joints	1
1–3 small joints	2
4–10 small joints	3
>10 joints (at least 1 small)	5
Serology (0–3)	
Neither Rf nor ACPA positive	0
At least one test low positive titre	2
At least one test high postive titre	3
Duration of Synovitis (0–1)	
< 6 weeks	0
> 6 weeks	1
Acute phase reactants (0–1)	
Neither CRP nor ESR abnormal	0
Abnormal CRP or abnormal ESR	1

http://rawarrior.com

Differential Diagnosis

Infections - Parvovirus, hepatitis B, hepatitis C, HIV, rubella, lyme, post streptococcal arthritis, gonococcal arthritis

Other autoimmune diseases - lupus, Sjogren's syndrome, psoriatic arthritis, reactive arthritis, IBD related arthritis, vasculitis, sarcoidosis, PMR, and others

Crystal induced diseases - gout , pseudogout

Osteoarthritis

Lab Testing

Rheumatoid factor

Anti CCP antibody

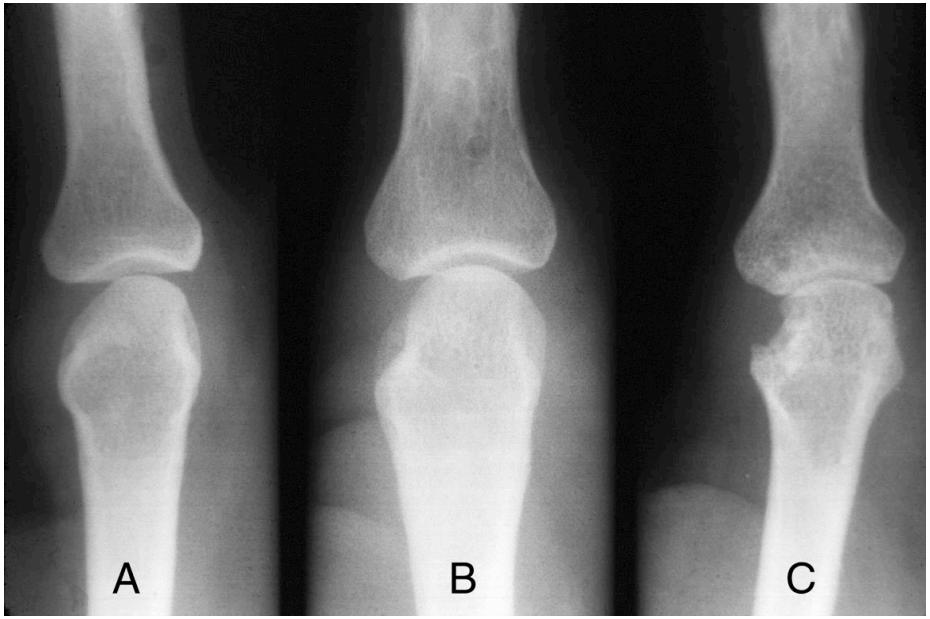
Anemia

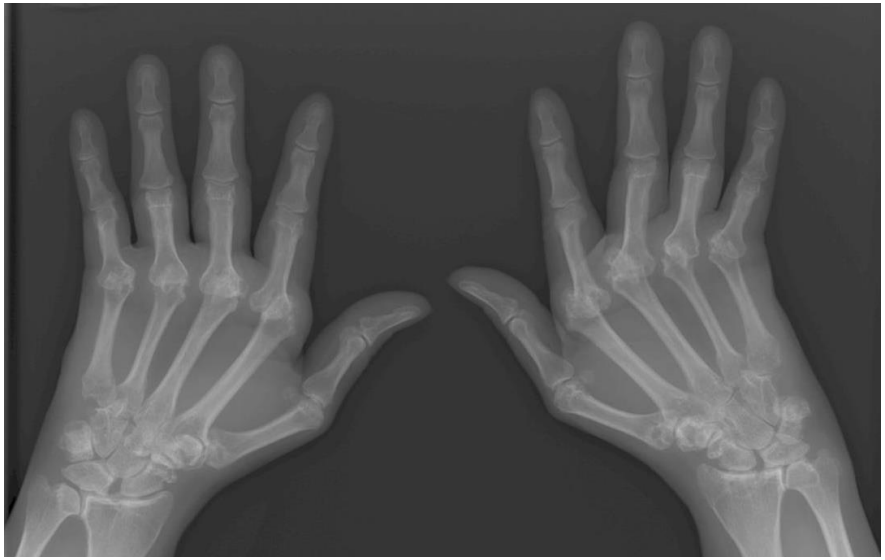
Elevated ESR / CRP

X-rays

Joint space narrowing

Erosions





MRI

Occasionally used in rheumatoid arthritis

Most helpful in early diagnosis

Ultrasound

Ultrasound can be used to show inflammation in the synovium or erosions in the bone

Prognosis

Individual variability

Elevated ESR and CRP

Elevated RF and anti CCP

X-ray evidence of erosions

Greater number of swollen and tender joints

Treatment

Why should you treat?

Relief of pain and fatigue

Restore quality of life

Prevent joint damage and disability

Prevent early coronary artery disease[18,19]

Non Pharmacologic Treatment

Diet

Exercise

Supplements

Acupuncture

Diet

Limited scientific data available[20,21,22,23,24,25]

Consider foods higher in omega fatty acids - flaxseed oil, walnuts, tofu, shrimp, kale, turnips, spinach, squash

Diet

Arthritis Foundation – Excellent resource for dietary recommendations

http://www.arthritis.org/living-with-arthritis/arthritis-diet/anti-inflammatory/rheumatoid-arthritis-diet.php

Exercise

Resistance exercises can be helpful[26]

Cardiovascular aerobic exercise programs can also be helpful[27,28]

Aquatic exercises, cycling, weights, walking

Supplements

Fish Oil / Flax[29]

GLA (Omega 6 fatty acid)[30]

Supplements

Turmeric (Curcumin)[31,32,33]

Boswellia[34]

www.arthritis.org

Acupuncture

Results from studies have been conflicting[35,36]

May be helpful

Pharmacologic Treatments

Analgesics

Nonsteroidal anti-inflammatories

Glucocorticoids

Non biologic DMARDs

Biologic DMARDs

Analgesics

acetaminophen / Tylenol

tramadol / Ultram

opioids (hydrocodone, oxycodone, morphine, etc...)

Marijuana (cannabinoids)[37]

NSAIDs

ibuprofen

naproxen

diclofenac

etodolac

sulindac

oxaprozin

meloxicam

indomethacin

piroxicam

nabumetone

ketoprofen

celecoxib

Glucocorticoids

Prednisone / methylprednisolone

Very helpful in relieving pain and inflammation

Extensive side effects

Short term use and low doses if possible

Edward Calvin Kendall (1886 - 1972)

Tadeus Reichstein (1897 - 1996)

Philip Showalter Hench (1896 - 1965)

Non Biologic DMARDs

hydroxychloroquine / Plaquenil

sulfasalazine / Azulfidine

methotrexate / Rheumatrex

leflunomide / Arava

gold / Auranofin

doxycycline

minocycline / Minocin

cyclosporine / Neoral

azathioprine / Imuran

Non Biologic DMARDs

Table 1. Oral DMARDs most commonly used to treat RA

Agent	Efficacy	Potential adverse effects	Advantages	Disadvantages	Use in pregnancy	Monitoring requirements
Methotrexate	Very effective at delaying radiographic progression of RA; the efficacy standard by which all other DMARDs are measured	GI complaints (eg, dyspepsia, nausea, anorexia, stomatitis), asymptomatic elevations in liver enzyme levels (risk of liver damage is low), myelosuppression, pulmonary toxicity	Favourable efficacy and toxicity profiles, low cost, weekly dosing regimen, established track record	Potential for hepatic, pulmonary, and haematological toxicity; need to abstain from alcohol during treatment; anxiety about taking a 'chemotherapy' drug	Contraindicated (class X); methotrexate is teratogenic and abortifacient	Measure liver enzyme and creatinine levels, and determine complete blood cell count every 4–8 weeks
Sulfasalazine	Almost as effective as methotrexate at delaying clinical and radiographic progression of RA	Nausea, vomiting, dyspepsia, anorexia, headache, rash, haematological disturbances (GI effects are reduced by use of enteric-coated formulation)	Long-term efficacy only slightly inferior to methotrexate, good side-effect profile	Twice-daily dosing	Generally safe (class B), although sulfasalazine may cause kernicterus if used near term	Determine complete blood cell count every 2–4 weeks for first 3 months
Hydroxychloroquine	Has not been proved to delay radiographic progression of RA, but early use does significantly reduce signs and symptoms of disease	Rash, abdominal cramps and diarrhoea (all infrequent); severe adverse retinal effects (extremely rare)	Extremely safe and well tolerated; does not require laboratory monitoring	Patients' concern about potential effect on vision	Category C	Baseline ophthalmological examination and either yearly examinations thereafter for all (ACR) or yearly examinations for high-risk patients (AAO)
Leflunomide	Comparable to that of methotrexate and sulfasalazine	Diarrhoea, alopecia, elevated liver enzyme levels (although diarrhoea usually responds to symptomatic treatment and alopecia is usually transient)	Efficacy is comparable to that of methotrexate; active metabolite can be removed with cholestyramine in case of pregnancy or severe toxicity	Various possible adverse effects, lack of long-term clinical experience	Contraindicated (class X); known teratogen	Measure liver enzyme and creatinine levels and determine complete blood count every 4–8 weeks

DMARDs = disease-modifying anti-rheumatic drugs; RA = rheumatoid arthritis; GI = gastrointestinal; ACR = American College of Rheumatology; AAO = American Academy of Ophthalmology.

Long history of use

Most are taken orally

Less expensive than biologic DMARDs

Risks are clearly known

Antibiotics

Doxycycline and minocycline[38-40]

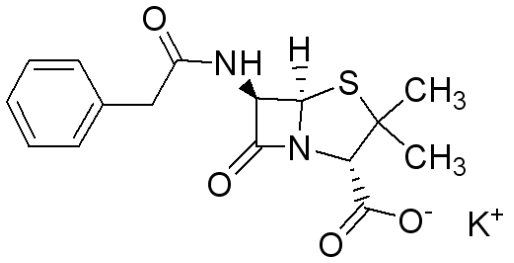
Most common side effects: skin, gastrointestinal

Antibiotics

Clarithromycin[41]

Roxithromycin[42]

Levofloxacin[43]



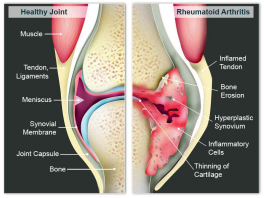
Biologic DMARDs

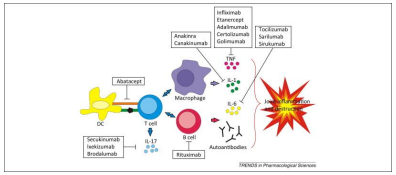
Advances in molecular biology led to the development of these medications

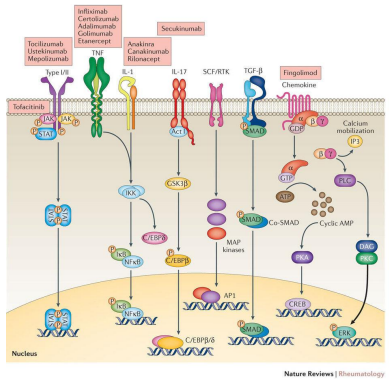
Targeted therapy

Main targets presently including anti TNF, anti IL6, B cells, T-cell costimulation, JAK inhibition

Targets in RA







Biologic DMARDs

Etanercept / Enbrel (1998)

Infliximab / Remicade (1998)

Anakinra / Kineret (2001)

Adalimumab / Humira (2003)

Abatacept / Orencia (2006)

Rituximab / Rituxam (2006)

Golimumab / Simponi or Simponi Aria (2009)

Certolizumab / Cimzia (2009)

Tocilizumab /Actemra (2010)

Sarilumab / Kevzara (2017)

Advantages

Very effective at relieving symptoms

Improve quality of life

Prevent joint damage

Minimal side effects

Disadvantages

Cost

Administered by injection or intravenously

Rare, but potentially serious adverse effects

Tofacitinib / Xeljanz

Approved in 2012

JAK inhibitor

Tablet

Taken 1-2 x / day

Sarilumab / Kevzara

FDA approval May 2017

IL6 receptor antagonist

Used as monotherapy or in conjunction with DMARDs

More effective than adalimumab as monotherapy

Biosimilars

Highly similar molecules to branded products

Same clinical effect, safety, route of administration, dosing

Potential for cost savings

For further info: pfizerbiosimilars.com

infliximab – dyyb / Inflectra

Infliximab – abda / Renflexis

etanercept – szzs / Erelzi

adalimumab – atto / Amjevita

Biosimilars

Cost

Insurance

Patient financial support

Interchangeability

INFLECTRA
INFLIXIMAB

MERCK
RENFLEXIS™
(infliximab-abda) for injection 100 mg

Erelzi™
(etanercept-szzs)

RA Med Resources

www.webmd.com/rheumatoid-arthritis/guide/rheumatoid-arthritis-medications

www.arthritis.org/about-arthritis/types/rheumatoid-arthritis/treatment.php

www.uptodate.com (search for rheumatoid arthritis treatments)

www.hopkinsarthritis.org/arthritis-info/rheumatoid-arthritis/ra-treatment

Medications

Severity of the disease

Time to onset of action

Concurrent medical illnesses

Safety

Patient or physician preference

Cost / insurance coverage

Combination Therapy?

Combination therapy has been shown to be more effective than monotherapy [44-49]

Popular combinations are hydroxychloroquine, sulfasalazine, and methotrexate or anti TNF therapy with methotrexate

Duration of Therapy

Depends on the clinical course[50]

10% - long clinical remission

15 to 30% intermittent symptoms

chronic progressive disease

Future Therapies

Baricitinib, filgotinib, ABT-494

Sirukumab, Clazakizumab

More biosimilars

Mavrililumab

CF101

Conclusion

RA is a common disease

History, physical exam, labs, and x-rays lead to the diagnosis

Non pharmacologic and pharmacologic options exist for treatment

Final Thoughts!

Traditionally rheumatoid arthritis has been a progressively disabling disease, but treatments today relieve symptoms, restore quality of life, and prevent the damage that previously led to disability