Advances in the Diagnosis and Treatment of Rheumatoid Arthritis

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Disclosures

Member, National Commission on Certification of Physician Assistants Board of Directors

Objectives

Upon completion of this session, participants will be able to:

-utilize the latest diagnostic approaches when evaluating persons with rheumatoid arthritis.

-identify the currently approved medications for rheumatoid arthritis.

-describe the risks, benefits and expectations of biologics and small molecule medications in treating rheumatoid arthritis.

References

Aletaha D, et al. 2010 Rheumatoid Arthritis Classification Criteria: An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. *Arthritis Rheum* 2010; 62; 2569-81.

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http://en.wikipedia.org/wiki/Egyptian_pyramids

Rheumatoid Arthritis

-0.5-1.0% of general population
  - -1% in Caucasians
  - -0.1% in rural Africa
  - -5% in Pima, Blackfeet and Chippewa Indians
  - -North>South in Northern Hemisphere
  - -Urban>Rural
  - -Family History increases risk X 3-5
  - -Heritability: 40-65% in SPRA, 20% in SNRA
- -Annual incidence-40/100,000

Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States- Part I. Arthritis & Rheum. 2008: 58(1):15-25.
A.J. Silman, M.C. Hochberg (Eds.), Epidemiology of rheumatic disorders, Oxford Univ Pr, New York (2001)

Rheumatoid Arthritis

-1.3 million adults with RA in US
-294,000 children in US with juvenile arthritis
-Occurs in females and males, but ♀>♂
-Lifetime risk
    -Female-1 in 28
    -Male-1 in 59
-Risk factors
    -Smoking
    -Low socioeconomic status
    -Low educational attainment
    -Periodontal disease (? *Porphyromonas gingivalis*)

Rheumatoid Arthritis

Cost

$140 B national arthritis-attributable medical costs in 2013 (CDC)

vs.

$80.2 B for direct medical cancer costs in 2015 (AHRQ)

-$164 B total national arthritis attributable lost wages in 2013 (CDC)

-6 Xs more likely to incur medical charges independent of RA (CVD, infxn, mental health, malignancy)

https://www.cancer.org/cancer/cancer-basics/economic-impact-of-cancer.html
https://www.cdc.gov/arthritis/data_statistics/cost.htm
Both accessed 25 July 2018

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HISTORY	Inflammatory Prototypical (RA)	Non-inflammatory Prototypical (OA)
SWET	+++	+
AM stiffness	+++	+
Aggravating Sxs	Rest	Activity
Alleviating Sxs	Activity	Rest
Extra-articular manifestations	+++	-
EXAM		
SWET	+++	+
ROM	+	+
Extra-articular manifestations	+++	-

Reprinted from
ARTHRITIS AND RHEUMATISM
Vol. 31, No. 3, March 1988

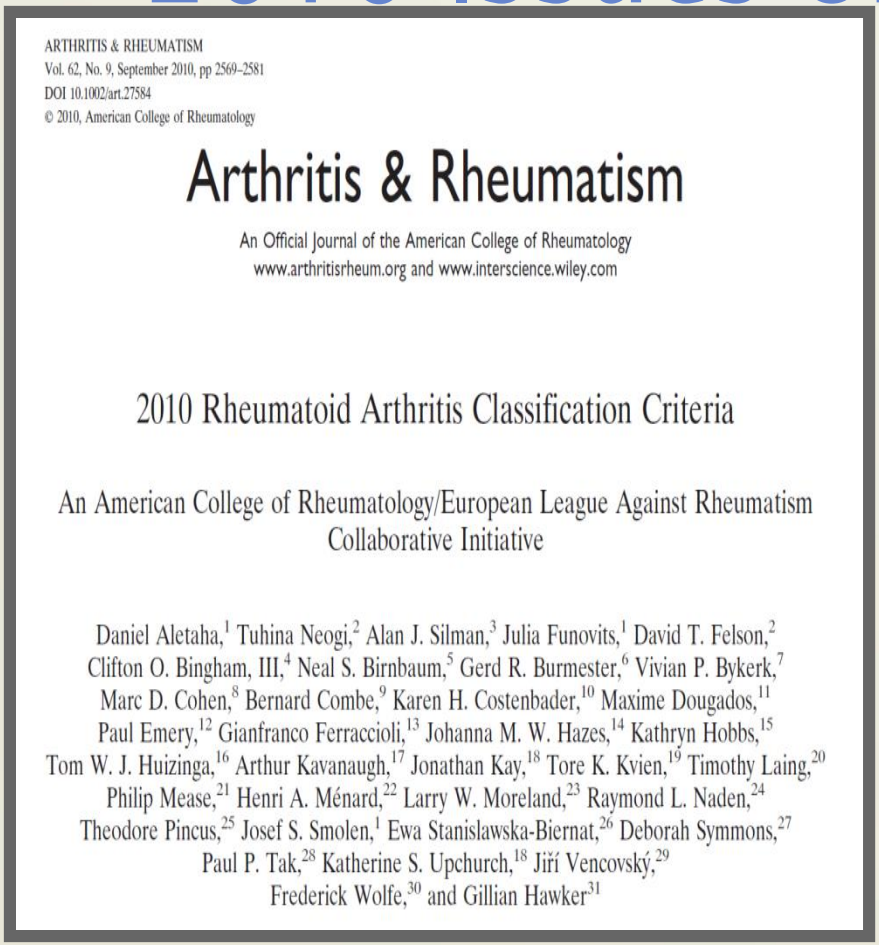
THE AMERICAN RHEUMATISM ASSOCIATION 1987 REVISED CRITERIA FOR THE CLASSIFICATION OF RHEUMATOID ARTHRITIS

FRANK C. ARNETT, STEVEN M. EDWORTHY, DANIEL A. BLOCH, DENNIS J. McSHANE, JAMES F. FRIES, NORMAN S. COOPER, LOUIS A. HEALEY, STEPHEN R. KAPLAN, MATTHEW H. LIANG, HARVINDER S. LUTHRA, THOMAS A. MEDSGER, Jr., DONALD M. MITCHELL, DAVID H. NEUSTADT, ROBERT S. PINALS, JANE G. SCHALLER, JOHN T. SHARP, RONALD L. WILDER, and GENE G. HUNDER

***Morning stiffness lasting at least 1 hour**
***Arthritis of three or more joint areas**
***Arthritis of hand joints**
***Symmetric arthritis**
***Rheumatoid nodules**
***Serum rheumatoid factor**
***Radiographic changes**

4/7 criteria present (first four listed for at least 6 weeks)

Published in the September 2010 Issues of *A&R* and *ARD*



ARTHRITIS & RHEUMATISM
Vol. 62, No. 9, September 2010, pp 2569–2581
DOI 10.1002/art.27584

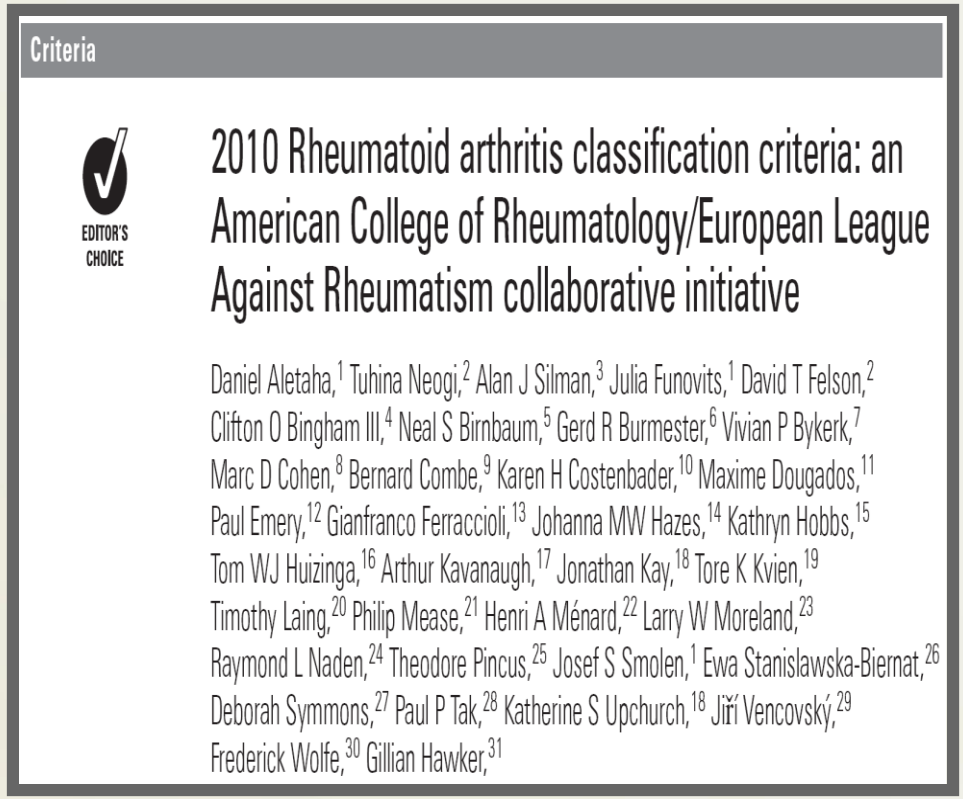
Arthritis & Rheumatism

An Official Journal of the American College of Rheumatology
www.arthritisrheum.org and www.interscience.wiley.com

2010 Rheumatoid Arthritis Classification Criteria

An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative

Daniel Aletaha,[1] Tuhina Neogi,[2] Alan J. Silman,[3] Julia Funovits,[1] David T. Felson,[2] Clifton O. Bingham, III,[4] Neal S. Birnbaum,[5] Gerd R. Burmester,[6] Vivian P. Bykerk,[7] Marc D. Cohen,[8] Bernard Combe,[9] Karen H. Costenbader,[10] Maxime Dougados,[11] Paul Emery,[12] Gianfranco Ferraccioli,[13] Johanna M. W. Hazes,[14] Kathryn Hobbs,[15] Tom W. J. Huizinga,[16] Arthur Kavanaugh,[17] Jonathan Kay,[18] Tore K. Kvien,[19] Timothy Laing,[20] Philip Mease,[21] Henri A. Ménard,[22] Larry W. Moreland,[23] Raymond L. Naden,[24] Theodore Pincus,[25] Josef S. Smolen,[1] Ewa Stanislawska-Biernat,[26] Deborah Symmons,[27] Paul P. Tak,[28] Katherine S. Upchurch,[18] Jiří Vencovský,[29] Frederick Wolfe,[30] and Gillian Hawker[31]



Criteria

EDITOR'S CHOICE

2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative

Daniel Aletaha,[1] Tuhina Neogi,[2] Alan J Silman,[3] Julia Funovits,[1] David T Felson,[2] Clifton O Bingham III,[4] Neal S Birnbaum,[5] Gerd R Burmester,[6] Vivian P Bykerk,[7] Marc D Cohen,[8] Bernard Combe,[9] Karen H Costenbader,[10] Maxime Dougados,[11] Paul Emery,[12] Gianfranco Ferraccioli,[13] Johanna MW Hazes,[14] Kathryn Hobbs,[15] Tom WJ Huizinga,[16] Arthur Kavanaugh,[17] Jonathan Kay,[18] Tore K Kvien,[19] Timothy Laing,[20] Philip Mease,[21] Henri A Ménard,[22] Larry W Moreland,[23] Raymond L Naden,[24] Theodore Pincus,[25] Josef S Smolen,[1] Ewa Stanislawska-Biernat,[26] Deborah Symmons,[27] Paul P Tak,[28] Katherine S Upchurch,[18] Jiří Vencovský,[29] Frederick Wolfe,[30] Gillian Hawker,[31]

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Target Population of the Criteria

Two requirements:

(1) Patient with at least one joint with definite clinical synovitis (swelling)

(2) Synovitis is not better explained by "another disease"

Differential diagnoses differ in patients with different presentations.

If unclear about the relevant differentials, an expert rheumatologist should be consulted.

2010 ACR/EULAR Classification Criteria for RA

JOINT DISTRIBUTION (0-5)	
1 large joint	0
2-10 large joints	1
1-3 small joints (large joints not counted)	2
4-10 small joints (large joints not counted)	3
>10 joints (at least one small joint)	5
SEROLOGY (0-3)	
Negative RF AND negative ACPA	0
Low positive RF OR low positive ACPA	2
High positive RF OR high positive ACPA	3
SYMPTOM DURATION (0-1)	
<6 weeks	0
≥6 weeks	1
ACUTE PHASE REACTANTS (0-1)	
Normal CRP AND normal ESR	0
Abnormal CRP OR abnormal ESR	1

≥6 = definite RA

What if the score is <6?

Patient might fulfill the criteria…

→ **Prospectively** over time (cumulatively)

→ **Retrospectively** if data on all four domains have been adequately recorded in the past

Definitions

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Definition of "JOINT INVOLVEMENT"

- Any swollen **or** tender joint (excluding DIP of hand and feet, 1st MTP, 1st CMC)
- Additional evidence from **MRI / US** may be used for confirmation of the clinical findings

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Definition of "SMALL JOINT"

MCP, PIP, MTP 2-5, thumb IP, wrist

NOT: DIP, 1st CMC, 1st MTP

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ACUTE PHASE REACTANTS (0-1)	
Normal CRP AND normal ESR	0
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Definition of "LARGE JOINT"

Shoulder, elbow, hip, knee, ankles

≥6 = definite RA

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Definition of "<u>>10 JOINTS</u>"

- At least **one** small joint
- **Additional joints** include: temporomandibular, sternoclavicular, acromioclavicular, and others (reasonably expected in RA)

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Definition of "SEROLOGY"

Negative: ≤*ULN* (for the respective lab)

Low positive: >*ULN but* ≤*3xULN*

High positive: >*3xULN*

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Definition of "SYMPTOM DURATION"

Refers to the patient's self-report on the maximum duration of signs and symptoms of any joint that is clinically involved at the time of assessment.

EXTRA-ARTICULAR MANIFESTATIONS OF RHEUMATOID ARTHRITIS

Skin	Nodules, fragility, vasculitis, pyoderma gangrenosum
Heart	Pericarditis, premature atherosclerosis, vasculitis, valve disease, and valve ring nodules
Lung	Pleural effusions, interstitial lung disease, bronchiolitis obliterans, rheumatoid nodules, vasculitis
Eye	Keratoconjunctivitis sicca, episcleritis, scleritis, scleromalacia perforans, peripheral ulcerative keratopathy
Neurologic	Entrapment neuropathy, cervical myelopathy, mononeuritis multiplex (vasculitis), peripheral neuropathy
Hematopoietic	Anemia, thrombocytosis, lymphadenopathy, Felty's syndrome
Kidney	Amyloidosis, vasculitis
Bone	Osteopenia

RA, splenomegaly, and neutropenia. This complication is seen in patients with severe, RF/ACPA-positive disease and may be accompanied by hepatomegaly, thrombocytopenia, lymphadenopathy, and fevers

Rheumatoid Nodules

ARS question

When following a person with RA, rheumatoid factors should be repeated with every lab draw so as to measure disease activity.

1-True.

2-False.

Rheumatoid Factor

- Autoantibodies directed against Fc portion of IgG (IgM to IgG)
- 75-90% of RA patients
- Result can aid in the diagnosis, but is not diagnostic of RA
- RF not used to measure RA disease activity, but higher titers can be associated with disease severity, erosions, extra-articular manifestations, disability

Rheumatoid Factor in other diseases

CH-Chronic disease
- *hepatic (PBC)
- *pulmonary (IPF, silicosis, asbestosis)

R-Rheumatoid Arthritis

O-Other rheumatic disease
- *SLE
- *Systemic sclerosis
- *MCTD
- *Sjögren's
- *Polymyositis
- *Sarcoid

N-Neoplasm, especially after XRT or chemo

I-Infections
- *AIDS
- *Mononucleosis
- *Parasitic infections
- *Chronic Viral
- *Hepatitis B/C
- *Chronic bacterial (SBE, syphilis, mycobacteria)

C-Cryoglobulienmia (esp with Hep C)

Anti-Cyclic Citrullinated Peptide Antibodies (anti-CCP)

- RA sensitivity 47-76%
  specificity 90-96%

- Can occur in active TB, SLE, Sjogren's, Polymyositis, Dermatomyositis, Scleroderma

- (+) CCP Ab
  more likely to have aggressive disease and progressive radiographic joint damage

Radiographic Studies

X-rays

Ultrasound

Magnetic Resonance Imaging

X-ray evaluation

	Inflammatory (RA)	Non-inflammatory (OA)	Other
Ankylosis	Rare	-	+ (Seronegative Sponylo)
Alignment	++	+ (irregular)	
Bone density	++	-	
Sclerosis	-	++	
Osteophyte	-	++	
Periosteal	-	-	+ (Seronegative Sponylo)
Cartilage space	++ (sym)	+ (asym)	
Calcification (soft tissue)	-	-	+ (CPPD)
Cysts	Pseudocystic	Subchondral	
Distribution	PIP/MCP/carpal	DIP/PIP/1st CMC	
Erosions	+++	- ("Erosive OA")	
Swelling	+++ (fusiform)	++ (H&B nodes)	

X-ray Changes in RA

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Goals of RA treatment

-Relieve pain

-Reduce inflammation

-Protect articular structures

-Maintain function

-Control systemic involvement

Ruderman, Eric M., MD, Editorial Consultant. Management of Rheumatic Diseases in the Biologic Era. Coalition of Rheumatology Educators; 2008

Raoul Dufy

http://www.health.com/health/gallery/0,,20496769_12,00.html

http://catalogue.drouot.com/ref-drouot/lot-ventes-aux-encheres-drouot.jsp?id=1798473

Dr. F. Dudley Hart's ABCs of RA cures

A-accupunture, apple diet, auto-haemotheropathy, angora wool

B-bee venom, copper bangles, various baths

C-chemotherapy, copper salts, crows' meat, cobalt

D-doca and ascorbic acid, diet

E-extractions of teeth and other septic foci, ECT

F-fasting, fever, faith, fango

G-gin, guaiacum, gelatine, green-lipped mussel

H-heat, honey, hope, hypnotism, hayseed

I-insulin, iodine, inner cleanliness

J-induction of jaundice

K-vitamin K, kaolin compresses

L-Lourdes, love

M-mud, magnetism, moxibustion, mistletoe

N-nutmeg, nettles

O-oral and intra-articular olive and other oils

P-placenta extracts, prayer, procaine, polyvinyl clothing

Q-quinine substitutes

R-rhubarb, rest

S-speransky's pump, sulphur, spa therapy, seaweed

T-fresh or pregnant transfusions of blood, tiger balm

U-ultrasonics, anti-rheumatic underwear, urea

V-vitamins, vertebral manipulations, vaccines

W-standing inside a whale, earthworms, water

X-Xmas snow

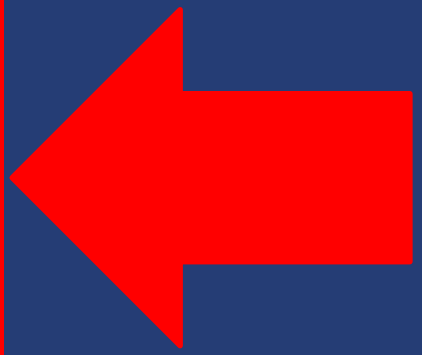
Y-Yoghurt, yoga

Z-zam-buk, zyloric (allopurinol)

Hart FD. History of the Treatment of RA. *British Medical Journal*. 1976; 1: 763-5.

Pharmacologic Therapy

- Nonsteroidal Anti-inflammatory Drugs
- Corticosteroids
- Hydroxychloroquine
- Sulfasalazine
- Methotrexate
- Leflunomide
- Azathioprine
- Cyclosporine



Disease modifying antirheumatic drugs (DMARDs)

Guidelines for use of glucocorticoids in RA

-Avoid use of glucocorticoids without DMARDs

-Prednisone, >10 mg/day, is rarely indicated for articular disease

-Taper to the lowest effective dose

-Use as “bridge therapy” until DMARD therapy is effective

-Remember prophylaxis against osteoporosis

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AMERICAN COLLEGE OF RHEUMATOLOGY

-Don't test ANA sub-serologies without a positive ANA and clinical suspicion of immune-mediated disease.

-Don't test for Lyme disease as a cause of musculoskeletal symptoms without an exposure history and appropriate exam findings.

-Don't perform MRI of the peripheral joints to routinely monitor inflammatory arthritis.

- Don't prescribe biologics for rheumatoid arthritis before a trial of methotrexate (or other conventional non-biologic DMARDs).

-Don't routinely repeat DXA scans more often than once every two years.

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-Don't routinely repeat DXA scans more often than once every two years.

Recommended laboratory evaluation for starting, resuming or significant dose increase for selected medications (RA pts)

THERAPEUTIC AGENTS	CBC	Transaminases	Creatinine	Other
HCQ	X	X	X	Eye exam
LEF	X	X	X	Hepatitis serologies if pt at risk
MTX	X	X	X	Hepatitis serologies if pt at risk
Minocycline	X	X	X	
SSZ	X	X	X	
Biologics	X	X	X	(Hepatitis serologies)

Saag KG, et al. American College of Rheumatology 2008 Recommendations for the Use of Nonbiologic and Biologic Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis. *ArthritisReum.* 2008; 59: 762-784.

Arthritis & Rheumatism (Arthritis Care & Research)
Vol. 59, No. 6, June 15, 2008, pp 762–784
DOI 10.1002/art.23721

SPECIAL ARTICLE

American College of Rheumatology 2008 Recommendations for the Use of Nonbiologic and Biologic Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis

KENNETH G. SAAG,[1] GIM GEE TENG,[1] NIVEDITA M. PATKAR,[1] JEREMY ANUNTIYO,[2] CATHERINE FINNEY,[2] JEFFREY R. CURTIS,[1] HAROLD E. PAULUS,[2] AMY MUDANO,[1] MARIA PISU,[1] MARY ELKINS-MELTON,[1] RYAN OUTMAN,[1] JEROAN J. ALLISON,[1] MARIA SUAREZ ALMAZOR,[3] S. LOUIS BRIDGES, JR.,[1] W. WINN CHATHAM,[1] MARC HOCHBERG,[4] CATHERINE MACLEAN,[5] TED MIKULS,[6] LARRY W. MORELAND,[7] JAMES O'DELL,[5] ANTHONY M. TURKIEWICZ,[1] AND DANIEL E. FURST[2]

Table 6. Recommendations for optimal followup laboratory monitoring intervals for complete blood count, liver transaminase levels, and serum creatinine levels for rheumatoid arthritis patients receiving nonbiologic disease-modifying antirheumatic drugs*

Therapeutic agents†	Monitoring interval based on duration of therapy		
	<3 months	3–6 months	>6 months
Hydroxychloroquine	None after baseline	None	None
Leflunomide	2–4 weeks	8–12 weeks	12 weeks
Methotrexate	2–4 weeks	8–12 weeks	12 weeks
Minocycline	None after baseline	None	None
Sulfasalazine	2–4 weeks	8–12 weeks	12 weeks

* More frequent monitoring is recommended within the first 3 months of therapy or after increasing the dose, and the outer bound of the monitoring interval is recommended beyond 6 months of therapy.
† Listed alphabetically.

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Biologics/Small Molecules

-Tumor Necrosis Factor-ά antagonists
- Adalimumab (Humira)-SQ
- Certolizumab (Cimzia)-SQ
- Etanercept (Enbrel)-SQ
- Golimumab (Simponi, Simponi Aria)-SQ, IV
- Infliximab (Remicade)-IV

-Interleukin-1 receptor antagonist (IL-1)
- Anakinra (Kineret)-SQ

-B cells
- Rituximab (Rituxan)-IV

-T cells
- Abatacept (Orencia)-SQ, IV

-Interleukin-6 receptor (IL-6R)
- Tocilizumab (Actemra) SQ, IV
- Sarilumab (Kevzara)-SQ

-Janus Kinase (JAK) inhibitor
- Tofacitinib (Xeljanz)-PO
- Baricitinib (Olumiant)-PO

My Pre-Drug Questions

-Current/recurrent infxns
-Cancer (CA)
-Congestive Heart Failure (CHF)
-Chronic Obstructive Pulmonary Disease (COPD)/asthma
-Tuberculosis (TB)
    *PPD hx
    *exposure
-Multiple Sclerosis (MS)
-Hepatitis B/C
-Hyperlipidemia

Biologics/Small Molecules

Pre-drug screening

-CXR

-PPD/Interferon-gamma release assays (IGRAs)

-Pneumonia vaccine

-Influenza vaccine

-Hepatitis B and C serologies

Biologics/Small Molecules

Potential risks

- Injection site/infusion reaction
- Infection risk (bacterial, TB/other granulomatous, opportunistic)
- Malignancy risk ?
- Demyelinating Disease, MS or Family Hx
- Heart failure
- Drug induced syndromes (ANA, dsDNA)
- Cytopenias
- Gastrointestinal perforation

Arthritis Care & Research
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DOI 10.1002/acr.22783

SPECIAL ARTICLE

2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis

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- -Recommendations for Early RA Patients
- -Recommendations for Established RA Patients
- -Recommendations for RA patients with High-risk comorbidities
  - *Congestive Heart Failure
  - *Hepatitis B/C
  - *Malignancy
  - *Serious Infections

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Recommendations for the Use of Vaccines in RA patients on DMARD and/or biologic therapy biologic therapy

-In early or established RA patients aged 50 and over, we conditionally recommend giving the herpes zoster vaccine before the patient receives biologic therapy or tofacitinib for their RA.

-In early or established RA patients who are currently receiving biologics, we conditionally recommend that live attenuated vaccines such as the herpes zoster (shingles) vaccine not be given.

-In patients with early or established RA who are currently receiving biologics, we strongly recommend using appropriately indicated killed/inactivated vaccines.

When to Refer

Uncertain diagnosis

Confusing Lab Results

Uncomfortable with DMARDS or Biologic Use

Patient not responding

Erosions or other radiographic changes

Side effects

Objectives

Upon completion of this session, participants will be able to:

-utilize the latest diagnostic approaches when evaluating persons with rheumatoid arthritis.

-identify the currently approved medications for rheumatoid arthritis.

-describe the risks, benefits and expectations of biologics and small molecule medications in treating rheumatoid arthritis.

Lessons for Practice

-Rheumatoid Arthritis is a systemic, inflammatory condition. Generally, early diagnosis lends itself to a better prognosis.

-There are multiple pharmacologic treatment options to care for those with rheumatoid arthritis.

-Biologic DMARDS require a thorough prescreening process and appropriate, ongoing monitoring while taking these powerful medications.

The ACR's *Simple Tasks* Campaign