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Rheumatoid Arthritis: A Brief Review for the Primary Care Physician

Rheumatoid arthritis (RA) is a systemic polyarticular form of inflammatory arthritis of unclear etiology. It primarily involves the synovial joints and is commonly symmetric in presentation. Joint pain and swelling are most commonly seen in patients with this condition. The presence of autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs), which the anti-cyclic citrullinated peptide (CCP) falls under, are found in the majority of patients. Left untreated, there is a high risk of significant deformity and disability.

Over the past decade, much has been learned of the pathophysiology and treatment of RA. The development of disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and biologic agents has changed the disease course. Since it is less common to see RA patients with deforming joint complications and rheumatoid nodules due to the efficacy of these therapies, there has been a shift of emphasis toward diagnosing the disease much earlier. Multiple studies have shown that early intervention is critical for achieving optimal outcomes.[1] Medical practitioners are encouraged to recognize this and initiate an early plan of action.

This article will review the important features of RA, including its clinical manifestations and predisposing factors, and will present a summary of the differential diagnoses that mimic RA, the work-up and treatment of the disease, and one approach to the diagnosis of RA.

Epidemiology

The global prevalence of RA is approximately 0.24%.[2] However, in the United States, the estimates are believed to be higher at 0.5-1.0%.[3] In 2007, an estimated 1.5 million U.S. adults were affected by the disease, with prevalence of 9.8 per 1000 in women and 4.1 per 1000 in men.[4] In general, women are affected two to three times more often than men.[5] The average age of RA patients is 66.8 years.[6] According to the Rochester Mayo Clinic Population study, the lifetime risk of RA was estimated to be 4% among women and 3% among men.[4]

EXECUTIVE SUMMARY

There have been many advances in diagnosing rheumatoid arthritis (RA). Primary care physicians are seeing less of the characteristic deforming joint complications that are common late in the disease process. Early intervention is critical in achieving optimal outcomes for patients.

- Rheumatoid arthritis is a systemic polyarticular inflammatory arthritis that is intimately associated with autoantibodies, rheumatoid factor, and anti-CCP.
- Early diagnosis and treatment is essential in preventing complications and functional disability.
- Viral infections and other rheumatologic diagnoses may mimic the presentation of rheumatoid arthritis. Ruling out these diseases is a must prior to committing to the diagnosis of rheumatoid arthritis.
- Multiple medications can be used in the treatment of rheumatoid arthritis. Treatment to remission or a low disease state should be the goal of any regimen.
- In the United States, the prevalence of RA is estimated to be 9.8 per 1000 in women and 4.1 per 1000 in men with the average age nearly 67 years. The lifetime risk of RA has been estimated to be between 3-4%.
- Risk factors include (HLA)-DRB1 genes, cigarette smoking, and periodontal disease.
- The newer 2010 ACR/EULAR classification requires a point count of at least 6 out of a possible 10 for diagnosis of RA.
- The most commonly used tests are the serum RF, ACPA, ESR, and CRP. RF and anti-CCP antibodies are helpful in the diagnosis of RA and in prognostication.
- Treatment goals are to reach remission or low disease activity and to prevent functional decline and halt disease progression. Familiarity with DMARD therapy is an essential component of modern management.

Risk Factors

The underlying etiology of RA is still unclear. However, researchers have identified several risk factors believed to affect disease initiation. For example, the complex interaction between genetic factors and environmental exposures may predispose a patient to having the disease. The "shared epitope" encoded in the human leukocyte antigen (HLA)-DRB1 genes contributes to genetic susceptibility and is deemed to be the single most significant genetic risk factor for RA.[7] The strongest associations were found on the DRB1*0401 and DRB1*0404 alleles of the HLA class II genes.

Cigarette smoking is a significant risk factor for the development of RA. This has been true especially for those with the shared epitope gene. A recent meta-analysis that included 4552 patients found that the risk of developing RA increased by 26% (relative risk = 1.26) among those who smoked 1-10 pack-years compared to never smokers. This risk doubled among those with more than 20 pack-years[8] and is found to be highest among people with positive anti-CCP antibodies.

Infectious causes have been implicated through epidemiologic studies in the development of RA. One such pathogen is Porphyromonas gingivalis, the main etiologic agent for periodontitis. Patients with RA have been found to have a higher prevalence of periodontal disease (3.95%) compared to the general population (1%).[9] The underlying reason for this association has been attributed to the ability of *P. gingivalis* to express peptidyl arginine deiminase, an enzyme responsible for post-translational citrullination of arginine residues. The exposure to these citrullinated antigens predisposes one to develop anti-CCP antibodies, which are implicated in the pathogenesis of RA.[10]

Socioeconomic and occupational exposures may present as risk factors for RA. According to a nationwide study in Sweden, an increased standardized incidence ratio of 1.4-1.8 was found among male miners and quarry workers compared to other occupations.[11] Silica exposure among male smokers also has been linked to the development of RA.[12]

Clinical Manifestations and Classification Criteria

In most cases, RA presents insidiously and can develop over weeks to months before the diagnosis is confirmed. The predominant symptoms are pain, stiffness, and swelling of the peripheral joints.[13] The 1987 American College of Rheumatology (ACR) classification criteria for RA presents a brief summary of the important manifestations of the disease (*see Table 1*).

It should be noted that the symptoms of morning stiffness and the finding of joint swelling should preferably be present for at least 6 weeks in classifying patients for RA. The reason is that several clinical entities may mimic a typical RA presentation, especially early in the disease process (see differential diagnosis section). Most infectious mimics of RA are self-limited and would resolve in around 6 weeks. However, patients with early or very early presentations of RA could be overlooked, as the 1987 criteria lacked the sensitivity to identify them.[14] This is especially true since one would not expect complications such as rheumatoid nodules and radiographic changes (periarticular osteopenia and bone erosions, *see Figures 1 and 2*) early on in the disease. Because of the inadequacies found on the 1987 ACR criteria, the ACR and the European League Against Rheumatism (EULAR)

brought forth a new criteria set for the classification of RA in 2010.[14] The new criteria try to reflect the evolving knowledge in the pathogenesis and treatment of RA and the need to identify the patients who have the disease early. The 2010 ACR/EULAR classification criteria are presented in Table 2.

Using the newer criteria, a patient would be classified as having definite RA if he/she has at least 6 points (out of possible 10). However, there are several caveats. First, the patient in whom RA is being considered needs to have at least one joint affected with definite signs of clinical synovitis (swelling, not just arthralgia/joint pain) that is not better classified by another disease. Second, the requirement in the previous criteria set of 6 weeks' duration was eliminated. Instead, a higher point was assigned if the patient's reported duration of symptoms is ≥ 6 weeks. Third, although some patients may not fulfill the criteria for definite RA, they may be reassessed and the criteria might be fulfilled cumulatively over time. These emphasize the need to diagnose and treat RA patients early.

The new criteria set also has brought into the spotlight several key laboratory tests aside from the RF. Elevation of either the erythrocyte sedimentation rate (ESR) or the C-reactive protein (CRP) gives a higher point total toward the classification of the disease. The ACPAs are part of the new criteria. This underscores the importance of these antibodies in the pathogenesis of RA.

The 2010 RA classification criteria are meant for classifying patients for research purposes rather than diagnosis. As RA may present in a variety of ways, it may not be possible to include all of these in one encompassing criteria set. Nonetheless, ACR and EULAR recognize that the criteria can be and likely will be

Table 1. 1987 Classification Criteria for RA

1. Morning stiffness Observed in and around the joints for at least 1 hour before maximal improvement
2. Arthritis of three or more joint areas Soft tissue swelling around the joint area as observed by a physician. Joint areas include the proximal interphalangeal, metacarpophalangeal, wrist, elbow, knee, ankle, and MTP joints
3. Arthritis of hand joints At least one swollen joint in the wrist, metacarpophalangeal, or proximal interphalangeal joint
4. Symmetric arthritis Simultaneous joint swelling observed on the same joint area on both sides of the body
5. Rheumatoid nodules These are subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, as observed by a physician
6. Serum rheumatoid factor
7. Radiographic changes Typical radiographic changes in rheumatoid arthritis include erosions or unequivocal bony decalcification localized in the involved joints
To classify a patient as having rheumatoid arthritis: Patient must satisfy at least 4 of the above criteria. Criteria 1 through 4 must be present for at least 6 weeks.
Adapted from: Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association. 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315-324.

Table 2. 2010 ACR-EULAR Classification Criteria for RA

	Points
A. Joint involvement	
1 large joint	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)	5
B. Serology (at least one test result is required)[1]	
RF (-) and anti-CCP (-)	0
Low titer RF (+) or low titer anti-CCP (+)	2
High titer RF (+) or high titer anti-CCP (+)	3
C. Acute-phase reactants (at least one test result is required)	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms	
< 6 weeks	0
≥ 6 weeks	1
Requirement for using the criteria: Patients should have at least 1 swollen joint (synovitis) that is not better explained by another disease.. To classify for rheumatoid arthritis: Add all the applicable points from each subgroup. A score of ≥ 6 is required for classification as definite RA.	
Adapted from Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010;62:2569-2581.	

used by providers as a diagnostic aid or to enable access to a particular intervention.

Differential Diagnosis

The differential diagnosis of RA is broad. Several clinical entities share the same features with RA, so they must be excluded prior to committing to the diagnosis.

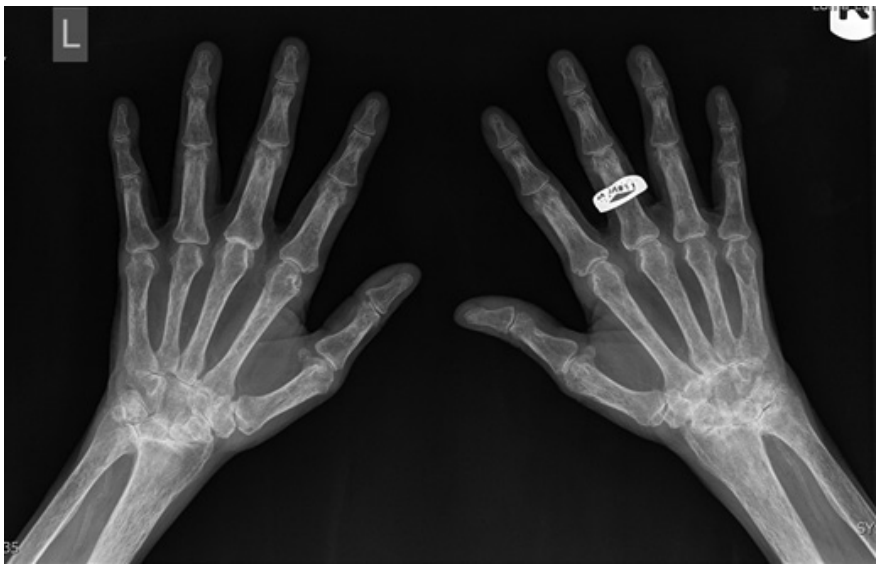
Viral Infections

Rubella. Rubella is acquired through inhalation of infectious aerosols and has an incubation period of around 14 days. In children, the first manifestation usually is the characteristic maculopapular rash, which is pruritic and occurs 14-17 days after exposure. The rash may start on the face and later spread to the lower half of the body. Lymphadenopathy in the head and neck also are common in children. On the other hand, the infection in adults tends to be of longer duration.[15] Arthritis is more common in adults and usually involves the knees, wrist, and fingers. However, it should be noted that arthralgias and arthritis are not considered complications of rubella but are an integral part of the disease presentation.[16]

Parvovirus B19. Parvovirus B19 infects only humans. The symptoms vary depending on age and overall health.[17] In children, it presents as a mild febrile illness with a rash (erythema infectiousum). In adults, swollen and painful joints are common and may look like the initial presentation of RA. The arthritis is usually symmetric, involving the small joints of the hands (especially the proximal interphalangeal and metacarpophalangeal joints), wrists, knees, and feet.[18] The difference between RA and parvovirus B19 infection is that 75% of patients with the infection eventually will develop a rash and the arthritis is self-limiting. In a majority of patients, the disease resolves in 2 weeks.[18]

Figure 1. Patient with long-standing RA

Radiographs of the hands show joint space loss especially on the metacarpophalangeal, radiocarpal, radioulnar joints. There is also ankylosis of the carpal bones on both hands. Note the diffuse osteopenia seen on this xray.



From the Loma Linda University Rheumatology Teaching File

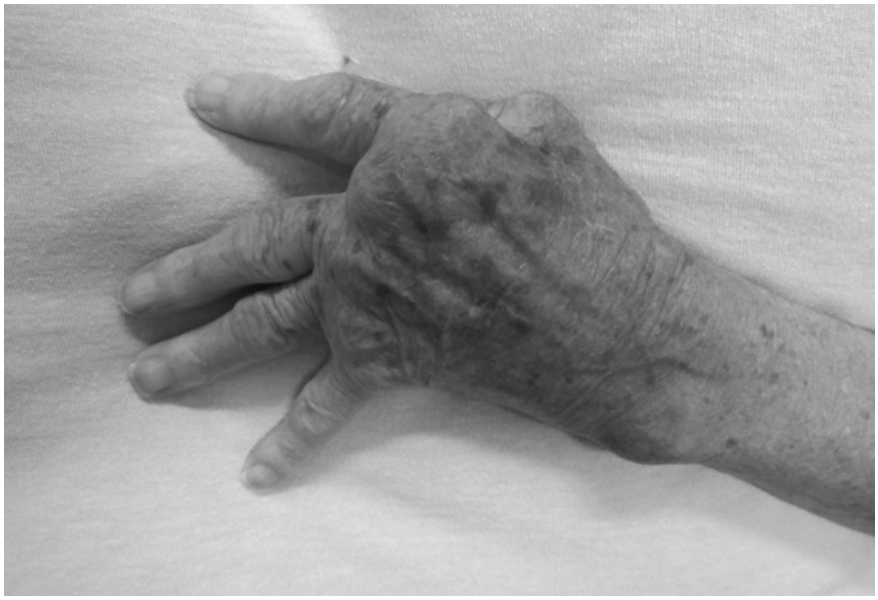
Hepatitis B. Infection with hepatitis B virus (HBV) can result in extrahepatic manifestations. The underlying etiology is believed to be immune mediated. A serum-sickness like prodrome is seen in approximately one-third of patients acquiring HBV and presents with arthritis and rash. This prodrome would spontaneously resolve at the onset of clinical hepatitis with few significant sequelae.[19] Joint destruction is rare.

Hepatitis C. Joint swelling is the most common extrahepatic manifestation of hepatitis C virus (HCV) infection. The underlying etiology of this is unclear but is thought to be a localized inflammatory reaction directed toward viral invasion or deposition of cryoglobulin-induced immune complexes in the synovial fluid.[20] The joint manifestation of HCV infection can be confused with that of RA. They both may present as symmetric arthritis, especially of the small joints. RF is generally positive in HCV infection but the anti-CCP would be negative. Also, the arthritis in HCV infection is non-deforming and associated with less morning stiffness, and rheumatoid nodules are less likely than is the case in RA.[20]

Rheumatic Diseases. RA may be difficult to differentiate from the presentation of other rheumatic diseases such as systemic lupus erythematosus (SLE), psoriatic arthritis (PsA), dermatomyositis, and mixed connective tissue disease. This is especially true during the first few months of the development of RA.[1] Differentiating these entities is tricky, but the main factors to consider are the extra-articular manifestations related to each disease. SLE may be accompanied by malar rash, oral ulcers, and positive serologic tests for antinuclear antibodies (ANA), anti-double-stranded DNA antibodies, and other autoantibodies. Dermatomyositis is associated with elevated serum creatine kinase

Figure 2. Patient with long-standing RA

Her left hand shows complications of rheumatoid arthritis such as ulnar deviation of the digits and intrinsic muscle wasting



Heilman, James, MD. Rheumatoid Arthritis. Digital image. Wikipedia, 07 Aug. 2010. Web. 22 May 2014.

and the characteristic rash on the face and neck along with proximal muscle weakness. The presence of psoriasis suggests a diagnosis of PsA. However, in about 20% of patients, the arthritis precedes the onset of the cutaneous lesions.[21] The joint involvement in PsA can present in a variety of ways, most commonly an asymmetric oligoarthritis. Other presentations can be RA-like distribution, arthritis mutilans, distal arthritis (affecting the distal interphalangeal joints), and spondyloarthropathy. Differentiating RA and PsA requires testing the RF and anti-CCP and eliciting a history of cutaneous lesions. A less common presentation of gouty arthritis can also be mistaken for RA, as the former may present as polyarticular synovitis. If gout is suspected, then joint aspiration with an assessment for presence of crystals is necessary. If suspecting other rheumatologic entities, a timely referral to a rheumatologist would be appropriate.

Laboratory Testing

Laboratory testing has been one of the cornerstones in the assessment of patients suspected of having RA. The most commonly used tests are the serum RF, ACPA, ESR, and CRP. RF and anti-CCP antibodies are helpful in the diagnosis of RA and in prognostication. The presence of these antibodies predicts which patients would be at high risk of functional decline and radiographic progression. They are also known to be positive in approximately half of RA patients, even before the onset of clinical disease with a median interval of 4.5 years.[22] On the other hand, ESR and CRP are most helpful in estimating disease activity.

Rheumatoid Factor. As measured in most laboratories, RFs are IgM autoantibodies directed against the Fc portion of immunoglobulin G (IgG). These are present in 75-80% of RA patients at some point during the course of the disease.[23] The sensitivity of RF in RA is 69% and the specificity is 85%.[24] The specificity is quite low, as it may be present in a variety of other diseases such as HCV, Sjogren's syndrome, SLE, bacterial endocarditis, and tuberculosis among others.[25]

Anti-cyclic Citrullinated Peptides. Anti-CCP antibodies are detected through the ELISA method and have roughly the same sensitivity as RF at 67%. However, anti-CCP has the distinct advantage of having a higher specificity of 95%.[24] Although specific, this antibody can also be found in other diseases such as SLE, Sjogren's syndrome, and active tuberculosis. It should be noted, however, that anti-CCP positivity is rare in hepatitis C. This is in contrast to RF, which is fairly common in HCV infections. The combination of RF and anti-CCP positive tests increases the probability of true positives in the diagnosis of RA.[26]

Erythrocyte Sedimentation Rate. The ESR test has been used in a variety of settings; however, its utility lies mostly in following levels of inflammation. ESR values may correlate with disease activity in RA and thus have been incorporated in the Disease Activity Score 28 (DAS28) scoring instrument, which is used in approximating RA disease activity and is useful in monitoring patient response to medications. The pitfall of ESR, unfortunately, is that this test is nonspecific. Various factors such as age, hemoglobin level, renal function, and presence of infection affect the test values. Thus, care should be carried out in using this test.

C-reactive Protein. CRP is an acute phase reactant that is considered a sensitive indicator of inflammation. In low levels, it is present in atherosclerosis, diabetes mellitus, and obesity. In high levels, it

Table 3. American College of Rheumatology Recommendations on Use of Vaccines in RA Patients Starting or Currently Receiving DMARDs or Biologic Agents

	Pneumococcal	Influenza (Intramuscular killed vaccine)	Hepatitis B	Human Papillomavirus	Herpes Zoster
DMARD monotherapy[1]	✓	✓	✓	✓	✓
Combination DMARDs[2]	✓	✓	✓	✓	✓
Anti-TNF biologics[3]	✓	✓	✓	✓	Recommended to be given prior to initiation of treatment.[5]
Non-TNF biologics[4]	✓	✓	✓	✓	Recommended to be given prior to initiation of treatment.[5]

DMARDs = disease-modifying antirheumatic drugs; ✓ = recommend vaccination when indicated (based on age and risk); anti-TNF = anti-tumor necrosis factor.
[1]DMARDs examples: methotrexate, sulfasalazine, hydroxychloroquine, leflunamide among others.
[2]Combination DMARDs consists of combination of any of the above medications (usually methotrexate with another drug)
[3]Anti-TNF Biologics include adalimumab, certolizumab, etanercept, golimumab, infliximab
[4]Non-TNF Biologics include abatacept, rituximab, tocilizumab
[5]Live attenuated vaccines are not recommended to be given to patients already taking DMARDs or any biologic agent.

Adapted from Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res* (Hoboken). 2012;64:625-639.

may indicate bacterial infection or inflammation.[1] In RA, this may be used in the same way as the ESR to approximate disease activity using the DAS28 instrument. However, caution is advised because up to 40% of RA patients at presentation have normal ESR or CRP.[27]

Treatment

Several guiding principles should be followed in the treatment of patients with RA. The ACR and EULAR have published recommendations for the management of RA.[28,29] The following recommendations help ensure that the patient is likely to have a good and safe outcome during the course of treatment

Early Diagnosis and Treatment of RA. As seen in comparative studies, treatment of RA is more effective in controlling disease if started earlier.[1] This is especially important since avoiding functional decline and decreasing discomfort are major goals in treating RA. The treatment includes DMARDs, as they are able to modify the disease, as opposed to simply treating symptoms such as inflammation and pain.[30] A treat-to-target (i.e., low disease state) strategy should be used in RA therapy. Broadly, DMARDs can be divided into synthetic/traditional and biologic.[31]

Synthetic DMARDs include methotrexate, sulfasalazine, leflunomide, and hydroxychloroquine. Methotrexate has been considered the anchor and first-line drug for the treatment of RA. The ACR recommends that patients with early RA (< 6 months) be started on DMARD monotherapy if they have low disease activity or if they do not have poor prognostic features (i.e., RF/CCP positivity, erosions on x-rays). However, if these factors are present, a combination of multiple DMARDs would then be recommended.[27] Various combinations of synthetic DMARDs that include methotrexate have been found efficacious and safe. More recently, the so-called triple therapy (methotrexate, sulfasalazine, and hydroxychloroquine) was found to be possibly as effective as the combination of methotrexate and etanercept, a biologic DMARD.[32]

Biologic DMARDs include medications that target specific cytokines, receptors, or cell surface molecules in the pathophysiology of RA. They can be classified according to their mechanism of action: 1) tumor necrosis factor (TNF)-alpha inhibitors include the medications adalimumab, certolizumab pegol, etanercept, infliximab and golimumab; 2) the medication rituximab is a B-cell depleting monoclonal antibody that acts by targeting the CD20 cell surface molecule; 3) abatacept is a selective costimulation modulator targeting the the T-cell activation process; 4) anakinra is an interleukin-1 receptor antagonist; 5) tocilizumab is an interleukin-6 inhibitor; 6) tofacitinib, the most recently approved RA therapy, inhibits the Janus kinase pathway. These medications usually are given either through subcutaneous injection or via infusion (tofacitinib is the only oral agent). They are indicated for the treatment of RA either as monotherapy (except infliximab) or in combination with methotrexate.

Table 4. ACR Recommendations on Laboratory Evaluation for Patients Receiving Biologic and Nonbiologic DMARDs

	CBC	Liver Function Tests	Serum Creatinine	Hepatitis B and C Screen	Ophthalmologic Examination[1]
Hydroxychloroquine	✓	✓	✓		✓
Leflunomides	✓	✓	✓	✓	
Methotrexate	✓	✓	✓	✓	
Sulfasalazine	✓	✓	✓		
All biologic agents	✓	✓	✓		

[1]Ophthalmologic examination is recommended within the first year of treatment. Annual follow up recommended for patients who are of higher risk (e.g., liver disease, concomitant retinal disease, and age ≥ 60 years)

Adapted from Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum* 2008;59:762-784.

All of these medications have good efficacy and safety in the treatment of RA.

Screening for tuberculosis, HBV, and HCV prior to treatment. Infections, especially tuberculosis, are increased in patients taking DMARDs.[33] Thus, it is vital to screen for these diseases prior to treatment. The ACR recommends the tuberculin skin test or interferon-gamma release assay as the initial test in all RA patients starting biologic agents. If they are found to be positive, appropriate diagnosis and treatment for active or latent tuberculosis should then follow. Generally, biologic DMARDs can be used in patients with latent TB only if they are undergoing treatment and have done so for at least 1 month. The viral hepatitis status, whether positive or negative for active/chronic disease, should also be ascertained. Any biologic agent is not recommended for patients with untreated chronic hepatitis B, while etanercept may be used cautiously in patients with hepatitis C.[27]

Vaccination in patients starting or currently receiving DMARDs therapy. As DMARD agents can blunt response to vaccines, vaccination is recommended prior to receiving these medications. If they are already on DMARD therapy, several vaccines can also be given. Table 3 shows the recommendations from the ACR regarding vaccination in patients with RA.

Treatment goal is to reach remission or low disease activity. Treatment strategies should aim to prevent functional decline, improve comfort, and halt disease progression. These would be achieved only with tight control of disease activity. The rheumatologist should be the primary director of the RA patient's care as the specialist would have the experience and knowledge necessary to evaluate and adjust the treatment regimen according to the patient's needs. It is therefore recommended that patients be referred in a timely fashion to a rheumatologist, which allows for the diagnosis to be confirmed and an appropriate plan of care started. The primary care physician also plays a pivotal role and should share in the management of RA.[34]

Close monitoring for adverse effects of drug therapy. As with any other medications, the physician should observe for potential adverse effects or toxicity associated with DMARD therapy. Abnormalities in liver and renal function as well as bone marrow suppression can occur during DMARDs therapy. Table 4 shows the ACR recommendations regarding monitoring the side effects of these drugs.[35]

Approach to the Diagnosis of RA

Rheumatoid arthritis should be suspected in any patient presenting with swollen and/or tender joints (i.e., polyarthritis). A thorough history is important, with special focus on the number and location of joint pains and swelling, as well as the presence of morning stiffness and other associated symptoms. Medication history is obtained for use of analgesics, corticosteroids, or nonsteroidal anti-inflammatory agents and their effects on joint complaints. A personal history for the presence of symptoms compatible with psoriasis, spondyloarhtropathies, inflammatory bowel disease, and SLE is also sought. Infections or risk for infections such as HIV, hepatitis, or other acute viral illnesses are assessed during the visit as well.

Physical examination focusing on the joints is necessary to assess for any synovitis, joint limitation of motion, or any deformities. A quick search for any skin lesions (psoriatic rashes, malar or discoid rashes), rheumatoid nodules, or gout tophi is included in the examination.

Laboratory testing to support the history and physical examination includes complete basic chemistries, complete blood count, as well as ESR, CRP, RF, and anti-CCP.

Other evaluations that would also be considered are hepatitis screen (HBsAg, anti-HBc, anti-HCV) and testing for latent tuberculosis infection (Tuberculin skin test or any of the Interferon-Gamma Release Assays- Quantiferon-TB Gold test or T-Spot test). The latter tests would be helpful in ruling out conditions that potentially may cause contraindications to any potential treatments such as DMARDs.

Radiographic imaging of all the major joints is obtained. This will assess for any damage to the joints caused by the inflammation as well as serve as a baseline for disease monitoring. The radiographs will also be helpful in differentiating other forms of inflammatory arthropathies, such as psoriatic arthritis and crystal arthritis among others, as the changes found on these conditions are usually distinct from RA.

Other imaging modalities are also available to aid in the diagnosis of rheumatoid arthritis. Magnetic resonance imaging and musculoskeletal ultrasound of the affected joints can be used to detect subtle inflammatory changes. These modalities are found to be more sensitive than radiographs in detecting synovitis. These tests are becoming more available in many rheumatology offices and may be used to detect synovitis not seen on clinical exam.[36]

Risk factor assessment and counseling is also done during the visit. The most significant modifiable risk factor for development of RA is smoking. Education on the importance of smoking cessation is given to the patient. If they are considering cessation, appropriate referrals are provided. If the patient is obese or has metabolic syndrome, counseling on addressing these will also be included since obesity is a risk factor for poor remission rates in patients with longstanding RA treated with anti-TNF agents.[37]

Conclusion

Rheumatoid arthritis is a polyarticular inflammatory arthritis that demands early diagnosis and treatment for improved patient outcomes.

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CME Questions

1. A 38-year-old male presented to your clinic complaining of joint pains in both hands and wrists for the past 4 months. There is associated morning stiffness of around 30 minutes and he says that he occasionally noted swelling of the wrists. He has taken acetaminophen and naproxen but without relief. His history is significant for past use of intravenous drugs but he states that he has been clean for 2 years now. His aunt has rheumatoid arthritis and she is on methotrexate. He is worried that he has rheumatoid arthritis. On physical examination, you note mild tenderness on the metacarpophalangeal and wrist joints of both hands. However, there is no swelling felt. His laboratory examination showed normal complete blood counts and serum chemistries but he tested positive for rheumatoid factor and hepatitis C antibodies. Arthritis series radiographs were read as normal by the radiologist. What would be the best next step in the evaluation of this patient?
   a. Continue to observe patient for resolution of symptoms
   b. Obtain anti-cyclic citrullinated peptide testing
   c. Start methotrexate 15mg orally per week with daily folic acid supplementation
   d. Start a Medrol-dose pack and reevaluate in 2 weeks.
2. A 60-year-old female patient with known rheumatoid arthritis presents to your office for her annual physical examination. She states that her rheumatoid arthritis and high blood pressure is controlled. She feels well and has no complaints. Her only request is that you give her vaccines that she needs to protect herself. No significant abnormalities are found on her physical examination except for the ulnar deviation of her fingers on both hands. These seem unchanged from a year ago. There is no swelling found on any of her joints. She is taking methotrexate, folic acid, injectable etanercept, and lisinopril. What would be the most appropriate reply to her request?
   a. All vaccines are contraindicated as you are taking etanercept, a biologic agent against TNF.
   b. Since you just turned 60, we need to give you the herpes zoster vaccine today.
   c. We will administer the inactivated influenza vaccine when you return for a visit just before October this year.
   d. Stop all your RA medications for 6-8 weeks prior to your next visit so we can give you the influenza vaccine.
3. A 28-year-old female patient who is an immigrant from Southeast Asia was recently diagnosed with rheumatoid arthritis by her rheumatologist. She has had a trial of methotrexate for 2 months now but continues to complain of significant morning stiffness and swelling on her wrists and hands. During her rheumatology appointment, her doctor discussed with her that a biologic agent will likely need to be added to control her disease. However, she wanted to ask you first as she is concerned about the infectious complications. On further history, you found that one of her cousins in her home country had been treated with several antibiotics

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for at least 6 months for a lung infection. On testing, it was found that she has a positive Quantiferon test but her chest x-ray is negative. She has no symptoms of active TB. What would be the most appropriate step in the treatment of this patient?
   a. Start isoniazid, pyrazinamide, and ethambutol
   b. Start isoniazid and vitamin B6
   c. Start isoniazid and the biologic agent together
   d. Start the biologic agents right away to treat the RA and prevent joint disability

4. You decide to treat the last patient on Question 3 with anti-tuberulous drugs for 9 months. Her next question then is, "If all goes well, when can I start the biologic agent for my rheumatoid arthritis?" How would you reply?
   a. You need to complete 9 months of treatment for latent TB infection (LTBI) before any biologic agents can be started.
   b. After 3 months of treatment for LTBI, you may then proceed to have the biologic rheumatoid arthritis medication.
   c. Generally, biologic agents may be started after 1 month of continuous treatment with an appropriate LTBI treatment regimen. However, you still need to complete 9 months of this regimen to treat the infection.
   d. Please see an Infectious Disease specialist.

5. According to the new 2010 ACR-EULAR Classification Criteria, the presence of rheumatoid factor and/or anti-CCP antibodies is necessary for classifying a patient with rheumatoid arthritis.
   a. True
   b. False

6. What nonpharmacologic measures should patients with rheumatoid arthritis undertake to increase possibility of good outcomes?
   a. Smoking cessation
   b. Diet and exercise, weight management
   c. Compliance to medications and other treatment plans
   d. Appropriate vaccinations to prevent infections while taking DMARDs
   e. All of the above

7. Which laboratory examinations would need to be ordered every 3 months for all patients with rheumatoid arthritis for the purposes of toxicity monitoring for DMARDs?
   a. Complete blood count (CBC), liver function tests (LFT) and sedimentation rate (ESR)
   b. CBC, LFT, creatinine
   c. CBC, creatinine, C-reactive protein (CRP), ESR
   d. CBC, LFT, creatinine, hepatitis C screen
   e. CBC, LFT, creatinine, ESR, CRP, quantiferon testing

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