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NEW THERAPIES IN RHEUMATOID ARTHRITIS AND OSTEOPOROSIS

CLINICAL MANIFESTATIONS

Rheumatoid arthritis is a chronic systemic autoimmune disease that affects all populations around the world. Women are affected 2.5-3 times more commonly than men. The peak age of onset is in the fourth-fifth decade of life.

The classical symptoms are those of early morning stiffness and 'gelling' usually in small joints, i.e. MCP, PIP and MTP joints. Bilateral carpal tunnel syndrome may precede the joint symptoms by sometimes weeks to months. Sometimes a patient will also present with acute monoarthritis and infection or a crystal associated arthropathy needs to be ruled out.

Systemic features such as fever, weight loss, malaise and fatigue can antedate or occur when a patient is flaring with joint symptoms.

Listed below is table 1:

RITERION	DEFINITION
1. Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement
2. Arthritis of three or more joint areas	At least three joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints.
3. Arthritis of hand joints	At least one area swollen (as defined above) in a wrist, MCP, or PIP joint.
4. Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in item 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry).
5. Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta-articular regions, observed by a physician.
6. Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects.
7. Radiographic changes	Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify).

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PHYSICAL FINDINGS

Symmetric tenderness and joint swelling are very common physical findings. Fusiform synovial bogginess where the joint lining has a mushy and enlarged swollen appearance is quite typical and characteristic. Latter and advanced physical findings include the following:

Ulnar deviation of the fingers
Tendon laxity
Loss of flexion and extension of the wrist

A careful examination of the extremities should be performed for compression neuropathies to include carpal tunnel syndrome, as well as ulnar neuropathy and tarsal tunnel syndrome. There may also be secondary interosseous muscle wasting in the fingers.

Additional common physical findings include:

1. Large knee effusion, i.e. Baker's cyst, which can dissect into the calf and mimic a deep venous thrombosis.
2. Synovitis of the hip can cause a myriad of symptoms from acute thigh, groin or buttock pain. This can be quite difficult to diagnose and may often require imaging studies.

EXTRA-ARTICULAR MANIFESTATIONS

Extra-articular organ disease can be seen in approximately 50% of all rheumatoid arthritis patients at some time during the course of their disease. The following table is a list of some of the more common organ systems involved.

Skin	Rheumatoid nodules (25%-50%)
Hematologic	Normocytic normochromic anemia (25%-30%), thrombocytosis, thrombocytopenia, lymphadenopathy
Felty's syndrome	Splenomegaly with neutropenia, large granular lymphocytes, thrombocytopenia
Hepatic	Nonspecific transaminitis
Pulmonary	Pleural thickening, pleural effusions, pulmonary nodules, diffuse interstitial lung disease, BOOP, Caplan's syndrome, cricoarytenoid arthritis (pulmonary arteritis, PAH, shrinking lung)

Cardiac	Pericarditis, accelerated atherosclerotic disease, Valvulitis
Ophthalmologic	Keratoconjunctivitis sicca (10%-15%), episcleritis, scleritis, uveitis, ulcerative keratitis
Neurologic	Peripheral entrapment neuropathy, cervical myelopathy due to cervical spine subluxation
Muscular	Muscle atrophy, inflammatory myositis
Renal	Low grade membranous glomerular nephropathy, reactive amyloid
Vascular	Small vessel vasculitis, systemic vasculitis

The most common extra-articular symptom of rheumatoid arthritis is Sjogren's syndrome which is manifested by dryness of eyes and dryness of mouth and can occur in 30%-40% of patients.

Rheumatoid nodules tend to occur over pressure areas such as the extensor surfaces of the elbows, Achilles tendons, occiput of the scalp, the fingers and the ischial tuberosity.

Rheumatoid nodules typically are observed in patients who have high titer rheumatoid factors.

LABORATORY FINDINGS

The most commonly used studies to monitor rheumatoid inflammation are the **WSR** and **CRP**. These tend to be increased in patients who have active disease.

The rheumatoid factor and CCP antibody are two commonly used studies to help diagnose rheumatoid arthritis. The rheumatoid factor is present in about 80% of patients with rheumatoid arthritis. High titers are predictive of patients who have more active disease. The anti-cyclic citrullinated antibody (anti-CCP) is found in the majority of patients with rheumatoid arthritis. Citrulline is a non-naturally occurring amino acid generated by deimination of arginine residue on protein. The sensitivity of the anti-CCP antibody test for rheumatoid arthritis is 70%, but the specificity is 90%. 35% of patients who are rheumatoid factor negative at the onset of diagnosis are usually CCP positive. As with the rheumatoid factor test, high titer CCP positivity is prognostic of patients who tend to have a more aggressive disease.

RADIOLOGY

Conventional x-ray (CR) is not a good imaging test for the early diagnosis of rheumatoid arthritis. Findings of soft tissue swelling or effusion may be present on CR. However, joint space narrowing or erosions may not be seen until 6-12 months into the onset of symptoms.

Both ultrasound and MRI are more sensitive than CR. Ultrasound is safe and very precise in showing not only changes of synovitis but also increased vascular changes by Doppler flow activity.

MRI can more accurately show erosive changes that are present by months to a year that CR cannot detect. The presence of these erosive findings has been shown to correlate with a patient's clinical prognosis of disability. This helps to better stage a patient's disease and to provide more aggressive treatment at an earlier time.

TREATMENT

Our understanding of the pathogenesis of rheumatoid arthritis has dramatically changed in the past 10-15 years. Today we now establish individual clinical targets and goals to assess our patients that are both reasonable and realistic. We have useful laboratory, imaging and disease activity measurements that help guide our therapy.

The following table is a list of some of the disease modifying anti-rheumatic and biologic therapies:

TNF antagonists Etanercept Infliximab Adalimumab Certolizumab Golemumab	Injection site reaction, reactivation of latent TB, increased risk of serious bacterial and opportunistic infection, possible increased risk of lymphoma, rare occurrence of demyelinating disorders and lupus like syndromes	Periodic CBC	Question about prior history of TB exposure and screen with tuberculin skin testing; avoid in NYHA class III-IV heart failure
Kineret	Injection site reaction, neutropenia, increased risk of serious bacterial infection		Screen with tuberculin skin testing

Abatacept	Infusion reaction, increased risk of serious bacterial infection		Screen with tuberculin skin testing; use with caution in individuals with COPD because of an increased risk of adverse events and serious infections in this group; avoid live vaccines
Rituximab	Infusion reaction, increased risk of infection	Periodic CBC	Screen for viral hepatitis B infection
Actemra	Infusion reaction, increased risk of infection	Periodic CBC	Screen for viral hepatitis B infection

For the past 35-40 years most patients with active rheumatoid arthritis are initially treated with one or two of the following DMARD medications.

This would include the use of Methotrexate, Leflunomide and/or Plaquenil.

After a period of 2-3 months patients are assessed for both efficacy and toxicity. Those patients who are still demonstrating signs of active disease on physical exam and laboratory tests would then be evaluated for the use of biologic therapies.

Randomized double blind studies have shown that the combination of Methotrexate with any of the anti-tumor necrosis factor (anti-TNF) therapies is superior to using monotherapy alone with regards to improvement in both clinical symptoms and slowing x-ray progression.

TUMOR NECROSIS FACTOR ANTAGONISTS (ANTI-TNF THERAPIES)

This family of medications has dramatically changed the lives of our patients and the way we approach treating rheumatoid arthritis. These medications are designed to inhibit an important cytokine [TNF], which has been shown to be a very important inflammatory cytokine which regulates the production of other pro-inflammatory molecules like IL-1 and IL-6. These molecules not only participate in the pathogenesis of rheumatoid synovitis but also lead to cartilage degradation and osteoporosis.

Side effects include an increased risk of infection, usually respiratory. The risk of malignancy has not been well established in long term use with these medications and many of our patients who have had background malignancies can be safely administered these biologic therapies.

ABATACEPT, RITUXIMAB AND ACTEMRA

These more recent medications have also been very effective in the treatment of rheumatoid arthritis. Abatacept is a fusion protein which binds to the CD80/CD86 on the surface of antigen presenting cells thus preventing their binding to CD28 on T cells. This blockade of CD28 binding prevents T cell activation which is critical in the pathogenesis of rheumatoid arthritis.

Rituximab was initially approved for the treatment of non-Hodgkin's lymphoma. It is a chimeric anti-CD20 monoclonal antibody approved for the treatment of rheumatoid arthritis. Rituximab depletes B cells in the synovium and in the serum. B cells secrete rheumatoid factor and other autoantibodies which play an important part in the disease process. Immunoglobulin levels usually remain normal. The complete mechanism of action is not fully understood.

Actemra was approved in 2009 and is a monoclonal antibody against IL-6. This is an important cytokine in the pathogenesis of rheumatoid arthritis. Increased levels of IL-6 have been found not only in the serum but also in the joints of patients with active rheumatoid arthritis. Excess levels of IL-6 in patients with rheumatoid arthritis have more complications of cardiovascular disease and osteoporosis.

Each of these three medications are administered intravenously and usually require several months of therapy to demonstrate their efficacy.

CONCLUSION

Rheumatoid arthritis is a very complicated illness to diagnose and to manage. Today with these many new promising biologic therapies our patients are now including words in their vocabulary such as 'remission' and 'cure' that were previously unheard of 15 years ago.

There are still many new opportunities and challenges that face us. This includes diagnosing the disease at an earlier stage, as well as finding safer and less expensive therapies.

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