Continuing Education

Rheumatoid Arthritis: Disease Characteristics and Comparisons of Novel Treatments

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Learning Objectives

1. Describe the basic pathophysiology of rheumatoid arthritis and how this accounts for the available therapies.
2. Discuss the characteristic joint involvement of rheumatoid arthritis and how laboratory findings supplement the diagnosis.
3. List the two categories of disease-modifying treatments and how their mechanisms of action differ.
4. Name the novel therapies recently approved and their therapeutic category.
5. Provide at least two common precautions when using the newer biologic agents for rheumatoid arthritis.

Epidemiology

Rheumatoid arthritis (RA) is an autoimmune disorder that affects about 1% of the world's population. RA can occur at any age and it is 2-3 times more common in women. Environment and genetics are factors in the increasing prevalence of RA. Environmental factors include pulmonary disease, smoking, infectious agents (e.g. *Escherichia coli)*, and periodontal disease.[1] The incidence of RA has been shown to decrease due to the use of oral contraceptives. It is thought that estrogen has a protective effect on developing RA.[2] Human leukocyte antigen (HLA) on genes is seen in patients with RA. Patients with RA have HLA-DR4, HLA-DR1, or both. Patients with HLA-DR4 are four times more likely to develop RA than a patient with HLA-DR1 typing; however, these findings are not a complete determinant of RA.[1]

Table 1

Factors Affecting Rheumatoid Arthritis	
Genetic Factors for RA	**Environmental Factors for RA[1]**
HLA-DR4 HLA-DR1	Pulmonary Disease Smoking Infectious Disease Periodontal Disease Oral Contraceptive Use

Pathophysiology

RA is characterized by chronic inflammation of the synovial fluid in the joint that leads to proliferation of tissue. This proliferation of inflamed tissue is called pannus. The inflamed tissue will eventually invade the cartilage and bone surface resulting in destruction of the joint; however, the factors that start the inflammation is unknown.[1]

Since RA is an autoimmune disorder, the immune system plays a vital role in the pathophysiology of the disease. The immune system is broken down into two categories: humoral and cell-mediated. The humoral system is responsible for producing antibodies; however, antibodies in patients with RA are called rheumatoid factors. Anti-citrullinated protein antibody (ACPA) is a diagnostic antibody for patients with RA. Patients who develop this antibody before they develop symptoms of RA tend to have a poor prognosis. The complement system and antibodies result in the build-up of polymorphnuclear leukocytes which release, oxygen-free radicals, hydroxyl radicals, and cytotoxins that lead to cell tissue and bone damage. The cell-mediated immune system is responsible for the lymphocytes, leukocytes, and other messengers of the body. Leukocytes invade the synovium of the joint, resulting in synovitis. After this the synovium of the joint will proliferate leading to the activation of fibroblasts. This results in the destruction of connective tissue and bone destruction.[1]

The complement system can be activated by immunoglobins which results in phagocytosis, chemotaxis, and the release of lymphokines. These are all presented to a lymphocyte and the antigen is recognized by major histocompatibility complex protein on the lymphocyte, which stimulates the activation of T and B cells. The release of cytokines and costimulation results in the activation of T cells. Activated T cells can produce cytotoxins which can further the inflammation.[1]

Proinflammatory cytokines such as tumor-necrosis-factor (TNF) alpha, interleukin-1, interleukin-6, and interleukin-7 can help continue the inflammation seen in RA. They communicate directly with fibroblasts, chondrocytes, osteoclasts, and macrophages and produce metalloproteinases which results in the erosion of bone.[3]

Janus kinase (JAK), a tyrosine kinase, is responsible for monitoring leukocyte activation. JAK also plays a role in monitoring the production of cytokines and immunoglobins. Tofacitinib is an oral JAK inhibiting drug that was recently approved to treat RA symptoms.[1]

Prostaglandins, kinins, histamine, and other vasoactive substances also play a role in the inflammation associated with RA. They increase blood flow to the inflammation site resulting in erythema, pain, warmth, and edema. All of these factors contribute to the degradation of tissue, cartilage, and bone associated with RA.[1]

Table 2

Immune System Mediators	
Cell-Mediated Immune System	**Humoral Immune System[2]**
T cells are found predominantly in the synovial tissues	Rheumatoid Factor (RF)- serologic marker of RA and is related to the severity of the disease
Pro-inflammatory Cytokines: TNF-alpha, IL-1, and IL-6 keep the inflammatory process going	RF leads to activation of complement system and this results in the release of lysosymal enzymes, kinins, and oxygen-free radicals

In short, synovial tissue becomes the site of interaction between macrophages, T cells, and B cells in RA. Synovitis (proliferation of synovial tissue) increases the amount of synovial fluid in bone and cartilage. This increased amount of fluid and tissue productions will eventually result in cartilage and bone destruction.[2]

Clinical Presentation

RA is characterized by progressive and irreversible damage of the synovial-lined joints, which includes loss of joint space and decreased bone functionality. Symptoms of RA usually develop over the course of several weeks to months. Symptoms include joint pain and stiffness of more than six weeks duration. Morning stiffness lasting more than one hour, the duration of joint pain and swelling, and involvement of three or more joints are important predictors of the development of RA. Affected individuals may also experience fatigue, weakness, low-grade fever, and loss of appetite. Fatigue may occur and become more of a problem late in the afternoon. During RA flares, the onset of fatigue typically begins earlier in the day and usually subsides. Signs of RA may involve tenderness with warmth and swelling over affected joints usually involving hands and feet. Joint involvement most commonly tends to be symmetrical; however, early in the disease patients may present with an asymmetrical pattern that eventually develops into the classical presentation. Rheumatoid nodules may also be present. Muscle pain may precede the development of joint swelling or synovitis and generally, joint deformity is seen late in the disease. Chronic inflammation contributes to loss of range of motion, atrophy of muscles, weakness, and deformity.[1,4]

Joint Involvement

In RA, the joints most commonly affected are the small joints of the hands, wrists, and feet. Large joint involvement may also be seen in the elbows, shoulders, hips, knees, and ankles. Early RA is more typically characterized by involvement of the small joints of the hand. Patients usually experience joint stiffness in the morning and the duration of stiffness tends to be directly related with disease activity. The duration typically exceeds 30 minutes and may persist all day. Swelling of the joints may be visible or may be apparent only by palpation. Due to proliferation of soft tissues or fluid accumulation within the joint capsule, the swelling may feel soft and spongy. The swollen joint may appear erythematous and feel warmer than nearby surfaces of skin early in the disease. During the acute phase, hand RA involvement is characterized by pain, swelling, tenderness, and grip weakness. Subluxation (joint displacement), instability, deformity, and muscle atrophy are more characteristic of the chronic phase of RA. Several deformities can occur late in the disease, such as boutonniere deformity (hyperextension of the distal interphalangeal [DIP] joint and flexion of the proximal interphalangeal [PIP] joint) and swan neck deformity (hyperextension of the PIP joint and flexion of the DIP joint) are commonly associated with damage and dislocation of finger joints and tendons. Hand

deformities may alter normal hand function, reducing grip strength and making it difficult to perform daily activities.[1,4]

The knee is a common site for RA and can be involved with loss of cartilage, therefore causing instability and joint pain. Formation of a cyst behind the knee caused by synovitis of the knee joint is known as popliteal or Baker's cyst. As these cysts become tense and painful, they may rupture, producing a scenario much like thrombophlebitis. Chronic pain can lead to muscle atrophy, resulting in ligamentous structural changes of the knee, therefore causing instability. The metatarsophalangeal joints of the foot and ankle are commonly involved, and considered one of the first early signs of RA. Metatarsophalangeal joint involvement is painful and disabling, which can make walking difficult for patients. Lateral deviation of the digits or Hallux valgus, bunions, and callus formations may occur at the great toe due to pressure necrosis of the joint skin from shoe irritation. With long-standing RA, widening of the foot commonly occurs.[1,4]

Other areas that may become affected by RA include the shoulder, elbow, spine, jaw, chest, and hip joints. RA may also affect other organ systems as well. A summary of extraarticular manifestations is included in Table 3.[1,4]

Laboratory findings

Many abnormal laboratory findings are associated with RA consisting of elevated inflammatory markers, abnormal blood cell counts, and abnormal imaging of affected joints. Rheumatoid factor (RF) is associated with joint erosion in RA (especially small joints), and is elevated in roughly 80% of these patients. Anti-citrullinated peptide antibodies (ACPA) are elevated in roughly 70% of the RA population and is also associated with joint erosions. ACPA is highly specific to RA with a specificity of greater than 90%.[1,2,5]

Less specific inflammatory markers are also present in the RA population. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are typically elevated in these patients. Autoantibodies such as antinuclear antibodies and antineutrophilic antibodies can also be elevated in these patients, but this is only seen in about 30% of patients presenting with a diagnosis.[1,2,5]

Chronic RA also tends to present with abnormal blood counts that are either directly or inversely related to the severity of symptoms. Leukocytes are elevated in the inflamed joints early in the disorder, with the counts typically being between 5,000-100,000/mm^3 in the affected joint.[2] Leukocyte counts can also vary according to treatment. Methotrexate and corticosteroids may lower and raise the leukocyte counts, respectively.[1] Normocytic normochromic anemia can be seen in these patients, and has an inverse relationship to the level of activity of the disease.[1,5] Anemia of chronic RA is difficult to treat as it will not typically respond to iron therapy and can be exacerbated by chronic NSAID use. Platelet counts may also rise and fall in direct association to the disease activity, and immunosuppressant agents may exacerbate thrombocytopenia associated with RA.[1,5]

Imaging techniques are helpful in diagnosing and tracking the progression of RA and include X-ray, MRI, and ultrasonography. The most common of these techniques is X-ray radiography, which typically only reveals information about the skeletal abnormalities associated with RA such as osteopenia, loss of joint space, and joint erosions. MRI and ultrasound allow for more insight into the amount of inflammation, erosions of the joints, and early changes to the bone and marrow than radiographic imaging.[5]

Diagnosis

Current guidelines from the American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) focus on diagnosing rheumatoid arthritis before the disease progresses to a debilitating state.[6] Former guidelines focused on differentiating RA from other rheumatological disorders once the disease had progressed. The goal is to slow progression of RA by diagnosing RA early.

A patient that presents with ≥1 joint with definite synovitis that is not better explained by another condition is diagnosed using both clinical symptoms and laboratory findings. A standard scoring scale is applied to the symptoms in order to aid in the diagnosis, and the scale takes into account joint involvement, serology, acute-phase reactant levels, and duration of symptoms. A patient can receive a

score of 0-10, and a patient that receives a score of ≥6 can be considered to have definite RA. Patients that receive a score of <6 should not be diagnosed with RA, but this score does not limit a future diagnosis of definite RA. A chart of the scoring scale from the ACR/EULAR guidelines is provided in Table 4.

Table 3

Rheumatoid Arthritis: Extra-articular Manifestations[1,4]		
Constitutional Symptoms	Fever Weight loss Anorexia	Asthenia Malaise
Rheumatoid Nodules	Subcutaneous	Lung parenchymal
Cardiovascular	Vasculitis (coronary arteritis) Pericardial inflammation and effusion Myocarditis Mitral valve disease Conduction detects	
Pulmonary	Pleural effusions Interstitial fibrosis Arteritis	Pulmonary nodules Pneumonitis
Ocular	Keratoconjunctivitis sicca Scleritis	Episcleritis Conjunctivitis
Neurologic	Compression neuropathy (such as carpal tunnel syndrome) Mononeuritis multiplex Cervical myelopathy Central nervous system disease (stroke, seizure, hemorrhage, encephalopathy, meningitis)	
Skin	Distal leg ulcers Cutaneous vasculitis	Palmar erythema
Hematologic	Anemia Granulocytopenia Cryoglobulinemia	Thrombocytosis Eosinophilia Hyperviscosity
Renal	Glomerulonephritis Secondary amyloidosis	Vasculitis
Hepatic	Elevated liver enzymes	

Table 4

ACR/EULAR Scoring Scale for RA Diagnosis[6]	
Presentation	Score
Joint Involvement	
1 large joint	0
2-10 large joints	1
1-3 small joints	2
4-10 small joints	3
>10 joints (at least 1 small joint)	5
Serology	
(-) RF and (-) ACPA	0
Low (+) RF or low (+) ACPA	2
High (+) RF or high (+) ACPA	3
Acute-phase reactants	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
Duration of Symptoms	
<6 weeks	0
≥6 weeks	1

A few important points should be kept in mind when using the scoring scale provided by the ACR/EULAR guidelines. Small joint involvement is more indicative of RA than large joint involvement, because small joints are more often associated with rheumatoid arthritis than other rheumatologic conditions. Although the patient could receive a score of six without laboratory analysis being conducted, a patient should always undergo testing of serology and acute-phase reactants. Normal and abnormal CRP or ESR should be determined based on local laboratory standards of the laboratory conducting the analysis. Although the ACR/EULAR guidelines are focused on early diagnosis of RA, late diagnosis can also be made using these guidelines by utilizing patient history and evaluation.[6]

Prognosis and Evaluation

There are two basic methods to determine progression of RA through radiographic findings: the Sharp method and the Larsen method. The Sharp method takes into account erosions and joint space narrowing. In the Sharp van der Heidje method (updated Sharp method) erosions are given a score of 0-5 for each joint, and joint space narrowing is given a score of 0-4 for each joint. The total Sharp van der Heidje score is between 0 and 448. The Larsen method takes into account both joint erosions and space narrowing in a single score of 0-5 for each joint.[7]

Table 5

Comparison of the Sharp and Larsen Methods[7]			
Sharp van der Heidje (erosions)	**Sharp van der Heidje** (joint space narrowing)	**Larsen**	**Score**
Normal	Normal	Intact bony outlines and normal joint space	0
Discrete erosions	Focal narrowing	Erosion <1 mm diameter or joint space narrowing	1
Large erosions according to surface area involved	Reduction of <50% of joint space	One or more small erosions with diameter <1 mm	2
	Reduction of >50% of joint space	Marked erosions	3
Erosions over the middle of the bone	Ankylosis	Severe erosions, usually no joint space left, original bony outlines are partly preserved	4
Complete collapse	N/A	Disfigurement with bony outlines destroyed	5

Methods of predicting RA progression based on inflammatory markers have also been utilized and have particularly been beneficial in assessing the efficacy of pharmacological therapy in treating RA. A prominent test used to assess the correlation of inflammatory markers with disease progression is the DAS28, which can be assessed for both CRP and ESR. The DAS28 looks at 28 joints commonly affected by RA, and gives a grade based ESR or CRP, the Ritchie articular index (RAI), and a general health assessment rating. Studies have shown that DAS28 values of ≤ 3.2 are associated with a good improvement in radiological findings, values of $3.2 < x \leq 5.1$ are associated with moderate improvement, and values of >5.1 are associated with no improvement.[8]

Treatment

Various treatment options are available for the management of RA. Non-biologic disease modifying anti-rheumatic drugs (DMARDs), biologic agents, and anti-inflammatory medications all play an important role in the management of RA.[9,10]

DMARDs work by a variety of different actions such as alkylation, folate antagonism, calcineurin inhibition, and various others. The purpose of DMARD therapy is to slow the progression of the disease by hindering arthritic damage. The most commonly used DMARD is methotrexate, which works by folate antagonism.[9,10]

Biologic agents also work on a variety of different markers to slow the progression of joint destruction seen in RA. TNF-alpha inhibition is the most common mechanism of action for these

drugs, although drugs that block interleukin-1, interleukin-6, CD20 (B cell surface antigen), B7 protein (on antigen presenting cell), and JAK Kinase are also used. The blocking of these pathways results in symptom relief as well as retardation of arthritic damage.[9,10]

Corticosteroids and NSAIDs are also used in RA to help with symptom relief. NSAIDs are commonly given along with disease modifying therapy to aid in symptom relief, and corticosteroids can be given to lower inflammation quickly. Corticosteroids are typically only given for a short duration due to the long-term effects of adrenal suppression.[9]

Table 6: RA Treatment Options[10,14]

Drug Name	Place in Therapy	ADRs	Pregnancy	Administration
Disease-modifying antirheumatic drugs (DMARDs)				
Methotrexate (Trexall®)	Treat mild, moderate, or severe RA	Nausea, vomiting, liver damage, hepatic fibrosis, bone marrow suppression	Teratogenic, can decrease fertility; Pregnancy Category X	Injection and Oral
Hydroxychloroquine (Plaquenil®)	Treat mild RA	Nausea, stomach pain, retinal toxicity	Not well studied in pregnancy	Oral
Sulfasalazine (Azulfidine®)	Prevent joint erosion	Nausea, hepatitis, hemolysis, decreased sperm	Pregnancy Category B	Oral
Leflunomide (Arava®)	Decrease symptoms, joint damage, and improve function	Diarrhea, myelosuppression, liver damage, rash	Teratogenic and carcinogenic; Pregnancy Category X	Oral
Azathioprine (Azasan®)	Refractory RA	GI problems, hepatitis, bone marrow suppression	Pregnancy Category X	Injection and Oral
Biologic Agents				
TNF Inhibitors				
Adalimumab (Humira®) Certolizumab pegol (Cimzia®) Etanercept (Embrel®) Golimumab (Simponi®) Infliximab (Remicade®)	Decrease symptoms, can be more effective than methotrexate monotherapy; act faster than DMARDs	Injection site reactions, fever, back pain, hypotension, cytopenias, tuberculosis, lymphomas	Pregnancy Category B	Injection
Anti CD20 Antibody				
Rituximab (Rituxan®)	Used in patients who did not respond well to methotrexate and/or TNF inhibitors	Anaphylaxis and leuko-encephalopathy	Pregnancy Category C	Injection

Table 6: RA Treatment Options[10,14] (cont)				
Drug Name	**Place in Therapy**	**ADRs**	**Pregnancy**	**Administration**
IL-6 Inhibitor				
Tocilizumab (Actrema®)	Used in patients who did not respond well to methotrexate monotherapy; superior to adalimumab; improvement seen in just 2 weeks	Infusion site reactions, dyslipidemia, liver damage, and neutropenia	Pregnancy Category C	Injection
Costimulation Modulator				
Abatacept (Orencia®)	Monotherapy or in combination with DMARDs	Headache, dizziness, pneumonia, cellulitis, pyelonephritis	Pregnancy Category C	Injection
JAK Kinase Inhibitor				
Tofacitinib (Xeljanz®)	Used in combination with methotrexate or as monotherapy	Diarrhea, URTIs, liver damage, dyslipidemia, tuberculosis	Pregnancy Category C	Oral

Current guideline recommendations for the treatment of RA draw a distinction between whether the patient has early or established RA.[1,11] The goal of early RA therapy is low disease activity or remission in symptoms of RA. DMARD monotherapy is typically indicated if the patient has a lower disease activity or presents without features of a poor prognosis. Alternative therapy is typically used if the patient presents with high disease activity or features of a poor prognosis. Alternative therapy includes combination DMARD therapy, combination methotrexate and hydroxychloroquine therapy, or TNF inhibitors with or without methotrexate.[11]

More treatment options are recommended in patients with established RA therapy, but the goals of therapy remain the same as early RA. Patients with low disease activity without a poor prognosis should be started on DMARD monotherapy initially. Methotrexate, hydroxychloroquine, or leflunomide can be added if the patient does not achieve an adequate response to DMARD monotherapy. Substitution to or addition of a TNF-alpha inhibitor can be considered if the patient remains uncontrolled, and a non-TNF biologic can be considered if the patient experiences a serious adverse event to other therapy. Patients with a poorer prognosis or higher disease activity should begin treatment with either methotrexate or combination DMARD therapy. A patient can be switched to either abatacept, rituximab, another DMARD or a TNF-alpha inhibitor if an inadequate response is not attained, and a non-TNF alpha biologic can be used if the patient remains symptomatic or develops a serious adverse event to treatment.[11]

Over the years outcomes for RA have improved thanks to aggressive use of nonbiologic and biologic therapies. Newer drugs are being made to further improve outcomes and help lower the amount of drugs needed to help manage RA symptoms. Recently approved drugs

for the treatment of RA include TNF-alpha inhibitors, IL-6 inhibitors, and JAK kinase inhibitors. A summary of newer agents is provided below.

TNF-alpha Inhibitors

Several TNF-alpha inhibitors have been approved for the treatment of RA including etanercept, infliximab, adalimumab, certolizumab, and golimumab.[1] TNF-alpha inhibitors are currently recommended if a patient has experienced inadequate symptom improvement from DMARD therapy, and can be used as monotherapy or in combination with other RA medications.[11]

Golimumab (Simponi®) is a new human monoclonal antibody indicated for the treatment of adults with moderately to severely active rheumatoid arthritis, in combination with methotrexate.[13-17] Golimumab binds to human tumor necrosis factor alpha (TNF-α), thereby interfering with endogenous TNF-α activity including the induction of proinflammatory cytokines, expression of adhesion molecules necessary for leukocyte infiltration, and activation of neutrophils and eosinophils. Golimumab is administered subcutaneously (Simponi®) or intravenously (Simponi Aria®). The usual dosing schedule for golimumab is 50 mg subcutaneously (SQ) once per month, or 2 mg/kg intravenously (IV) at weeks 0 and 4, then every 8 weeks thereafter.[13-15] Efficacy and safety of switching between IV and SQ formulations have not been established.[13] Golimumab has a bioavailability of approximately 53% with a half-life elimination of approximately 2 weeks. The metabolism pathway of golimumab is still unknown. The effects of special populations such as hepatic and renal impairment on the pharmacokinetic parameters of golimumab have not been evaluated.[13-15]

The efficacy of golimumab has been evaluated in multicenter, randomized, double-blind, controlled trials in patients with moderately to severe active RA. In one trial, 445 patients with active RA previously treated with at least one dose of a TNF-blocker showed a 20% improvement in the American College of Rheumatology (ACR20) score at week 14 (primary endpoint). This was achieved in 40% of patients who received golimumab 50 mg plus methotrexate (n = 101) compared with 17% of patients who received placebo plus methotrexate (n = 103).[13,14,16] In another trial, 637 patients who had not previously received methotrexate or a TNF-blocker were evaluated, and a 50% improvement (ACR50) score at week 24 (primary endpoint) occurred in 40% of patients who received golimumab 50 mg plus methotrexate (n = 159) compared with 29% of patients who received methotrexate alone (n = 160). In conclusion, there was a greater percentage of patients in the combination therapy group that achieved reductions in ACR scores compared to methotrexate monotherapy.[13,14,16]

Common adverse reactions, reflective of the adult population, include upper respiratory infections, injection site reactions, and viral infections such as influenza and oral cold sores.[13-17] Due to the mechanism of action of golimumab, these adverse reactions are contributable from the possibility of affecting host defenses against infections, as TNF mediates inflammatory cytokines and modulates cellular immune responses.[13-15] Serious adverse effects with the use of golimumab include hypertension, dizziness, skin rash, leukopenia, increased liver enzymes, and viral infections, to name a few.[13-17] Although the safety profile of golimumab is similar to that of other TNFα inhibitors, it is found to be less likely to cause serious infections compared to other TNFα inhibitors such as certolizumab and infliximab.[17]

Anti-Interleukin 6 Antibodies

Anti-IL 6 antibodies made their debut with tocilizumab (Actemra®) in 2010.[18] IL-6 is associated with inflammation seen with RA, and tocilizumab works by blocking the IL-6 receptor, which results in decreased cytokine and acute phase reactant levels. Tocilizumab is indicated for moderately to severely active RA, as well as active polyarticular juvenile idiopathic arthritis and active systemic juvenile idiopathic arthritis.[19] Trials are currently assessing its efficacy in treating systemic lupus erythematous.[18] Tolicizumab is an injectable drug and can be given either intravenously (4 mg/kg every 4 weeks, max= 800 mg/dose) or

subcutaneously (≥100 kg= 162 mg every week, <100 kg= 162 mg every other week).[13,14] The efficacy of tocilizumab for RA has been assessed in multiple clinical trials and it is currently recommended in patients that have failed therapy with one or more DMARDs.[11,19]

A recent trial conducted by Dougados et al. (the ACT-RAY study) evaluated the efficacy of tocilizumab added to methotrexate compared to tocilizumab therapy alone over the course of 24 weeks in patients that had not achieved adequate response to methotrexate monotherapy.[20] The primary endpoint of the study was the DAS28-ESR remission rate, and several other remission rates were included for secondary endpoints. Combination therapy did not prove to be superior to tocilizumab monotherapy for the primary endpoint, and there were not clinically significant differences in the two arms regarding efficacy; however, there was an increased incidence of elevated transaminase levels in the combination therapy arm. A follow-up at week 52 of the ACT-RAY trial also found that radiographic changes between the two groups were very similar and the effect on transaminase levels continued to be elevated in the combination group.[20] The clinical significance of elevated transaminase levels in these patients was not assessed.

Tocilizumab is not significantly metabolized, which decreases the risk for drug interactions, and the most common adverse effects seen with tocilizumab are hypertension, headache, respiratory tract infections, elevations of hepatic transaminases, and increased lipid parameters.[13,14,19] More serious adverse effects include neutropenia and serious infections. These infections typically occur when the patient is receiving an immunosuppressive agent such as methotrexate or corticosteroids, which has led to a boxed warning for this effect. The boxed warning lists active tuberculosis, invasive fungal infections, and opportunistic viral and bacterial infections as a potential concern with tocilizumab therapy.[13] Guidelines recommend that patients undergo tuberculosis testing before administration.[11,19] Due to the serious adverse effects associated with this therapy, tocilizumab should be discontinued if the patient has hepatic transaminase levels that rise greater than five times the upper limit of normal, ANC levels that fall below 500 cells/mm^3, or platelet counts that fall below 50,000 cells/mm^3.[13]

A Japanese post-marketing surveillance study evaluated the safety and efficacy of tocilizumab in 7,901 patients receiving tocilizumab. Patients were followed over the course of 28 weeks.[22] The surveillance demonstrated that serious infections and abnormal laboratory tests (predominantly lipid abnormalities) were the most common serious adverse events. Most infections were respiratory infections, and four of which were tuberculosis. The study also found that patients that were ≥65 years of age, had longer duration of disease, had either previous or current respiratory disease, and were on a dose of corticosteroid >5 mg/day prednisolone equivalent were more likely to develop a serious infection. Patients followed in this study also demonstrated improvements in DAS28-ESR scores and EULAR Good Response rates. A 3-year, follow-up to the study, which included over 5,000 patients, revealed that the side effect profile of tocilizumab remained consistent up to a 3-year period.[23] The follow-up study also revealed that there was not an increased risk of death associated with the use of tocilizumab, and the risk of cardiac dysfunction decreased over time.

Although tocilizumab is the only current IL-6 inhibitor currently approved for RA, other anti-IL-6 antibodies are currently being investigated.[18,24] Sarilumab has recently completed a phase III trial (n= 1,369) in which it was being assessed for moderate to severe RA, and the trial showed a similar safety and efficacy profile to tocilizumab.[25] Sirukumab has completed a phase II study (n= 36), and appears to show similar efficacy to tocilizumab and lower rates of infection, although these findings still need to be assessed in larger trials.[24,26] Another antibody being assessed is olokizumab, which has completed a phase IIb trial (n= 221) that looked at patients that were uncontrolled on TNF inhibitors.[24,27] Olokizumab demonstrated a similar safety and efficacy profile to tocilizumab in this trial. Sarilumab, sirukumab, and olokizumab have all shown to be potential future therapies for RA.

JAK Kinase Inhibitors

Tofacitinib (Xeljanz®), an oral Janus kinase receptor inhibitor, was approved in 2012 for the treatment of RA.[28] These receptors are involved in signal transduction and regulation of gene expression. When these receptors are inhibited, cytokine-mediated gene expression and intracellular activity is declined.[30] There are a few different types of tyrosine kinase receptors such as: JAK1, JAK2, JAK3, and TYK2. Tofacitinib has a greater inhibition of JAK3 and JAK1 over JAK 2 and TYK2. [29] Tofacitinib has an FDA labeled dosing of 5mg by mouth twice daily. Tofacitinib can be given in combination with nonbiologic DMARDs, but should not be given with biologic DMARDs or strong immunosuppressants (e.g. tacrolimus, azathioprine, and cyclosporine). Tofacitinib should also be discontinued if the absolute neutrophil count (ANC) <1,000 cells/mm^3, if the hemoglobin <9g/dL, or if the absolute lymphocyte count <500 cells/mm^3. Tofacitinib is metabolized hepatically to inactive metabolites and is excreted renally.[14]

In a phase 3, double-blind, placebo-controlled, parallel-group trial tofacitinib versus placebo was compared for the treatment of RA. In this six month study, 611 patients were randomized based on a 4:4:1:1 ratio, to 5 mg of tofacitinib twice daily, 10 mg tofacitinib twice daily, placebo for 3 months followed by 5 mg of tofacitinib twice daily, or placebo for 3 months followed by 10 mg tofacitinib twice daily. The primary endpoints of this study were number of patients achieving ACR 20, the change in Health Assessment Questionnaire-Disability Index (HAQ-DI) and the amount of patients with a Disease Activity Score for 28-joint counts based on erythrocyte sedimentation rate (ESR) of less than 2.6 (DAS28-4[ESR]).[28]

In the tofacitinib group a higher percentage of patients achieved a 20% improvement in the ACR 20 versus placebo (59.8% in the 5mg, 65.7 in the 10mg tofacitinib group, and 26.7 placebo). Patients in the tofacitinib 5 and 10mg groups had a greater reduction in the HAQ-DI scores versus placebo (-0.50 and 0.57 points, respectively vs -0.19 points in placebo); however, the amount of patients with a DAS28-4[ESR] of less than 2.6 was not significantly different between tofacitinib and placebo. Compared to placebo, there was an increased amount of serious infections associated with tofacitinib. Some of the infections that patients experienced were cellulitis, liver abscess, bronchitis, tuberculous pleural effusion, and pyelonephritis. Headache and upper respiratory tract infections were common adverse effects, and increased levels of cholesterol levels and neutropenia were seen in patients treated with tofacitinib. In conclusion, tofacitinib was shown to be an effective monotherapy in decreasing symptoms and improving physical mobility in patients with RA versus placebo; more trials need to done to see how it compares to active therapies for RA.[28]

New drugs like tofacitinib are being marketed, in hopes of having a safer adverse effect profile. Methotrexate (MTX) is a first-line option for patients with RA; however, its safety profile leaves much to be desired. MTX is a folate antimetabolite that inhibits dihydrofolate reductase (DHFR).This enzyme is responsible for transferring carbons for purine, thymidylate, methionine, and DNA synthesis.[31] The risk of developing serious liver disease increases with duration and dose of therapy. A wide range of side effects are known to occur during MTX therapy such nausea, diarrhea, interstitial pneumonitis, fatigue, headache, opportunistic infections, anemias due to bone marrow depression, and death. Some studies have evaluated the efficacy and safety of tofacitinib compared to MTX in order to allow for a safer option in treating RA.[14]

In a trial that compared tofacitinib head-to-head with MTX, 958 patients were randomized based on a 2:2:1 ratio to receive either 5 or 10 mg of tofacitinib twice daily or methotrexate 10 mg/week (dose was increased by 5 mg/week every 4 weeks to 20 mg/week over 8 weeks). The coprimary endpoints were mean changes in the van der Heijde modified total Sharp score and the proportion of patients with an ACR 70 response. They looked at the reduction in the number of tender and swollen joints and improvement in three of five categories: the level of disability, C-reactive protein or erythrocyte sedimentation rate, patient's assessment of pain, global assessment of the

disease by the patient, and global assessment of the disease by the physician.[28]

Changes in the Sharp score were significantly smaller in the tofacitinib group versus the methotrexate group. Patients receiving 5 and 10 mg of tofacitinib had an ACR 70 response of 25.5% and 37.7%, respectively. Patients receiving methotrexate had a 12.0% ACR 70 response which was a significant difference between the groups. More patients developed herpes zoster and cancer when treated with tofacitinib versus methotrexate. Tofacitinib was also associated with increased levels in creatinine and cholesterol and decreased level of neutrophils. When compared to methotrexate, tofacitinib showed improvement in symptoms of RA, physical mobility and a reduction in damage progression. In conclusion, tofacitinib was superior to methotrexate for the treatment of RA in patients who were methotrexate-naive. This trial shows promising results for tofacitinib in the treatment of RA; however other trials need to be done to evaluate this new therapy versus biologic therapies.[28]

Looking to the future, newer JAK kinase inhibitors are in clinical trials in hopes of having similar benefits of treating RA like tofacitinib. Baricitinib a JAK inhibitor that is currently in Phase III clinical trials has specificity over JAK1 and JAK2 compared to JAK3 and TYK2. A promising trial on this drug shows that it will be effective in reducing symptoms in RA and it does not appear to have some of the adverse effects (herpes zoster and tuberculosis) like tofacitinib.[18,32]

Conclusion

Rheumatoid arthritis is a complex disease that can be very debilitating to patients that are experiencing its symptoms. RA is characterized by an immune-mediated response, which results in inflammation and destruction of synovial and skeletal tissue.[1,2] Joint involvement tends to be symmetrical and can affect many different sites including the hands and knees. Inflammatory markers such as RF, ACPA, ESR, and CRP can help determine the amount of inflammation that is present. To help decrease the inflammation, drugs like DMARDs, TNF inhibitors, and other biologics are being used. Newer therapies are providing several different mechanisms to achieve lower disease activity and/or remission in the progression of the disorder, and research is being conducted to expand upon these new mechanisms of action.[17]

Table 7

Summary of Approved Novel RA Therapies[12,13]			
Generic/ Brand Name	Golimumab (Simponi®)	Tocilizumab (Actemra®)	Tofacitinib (Xeljanz®)
Mechanism of Action	TNF-α Inhibitor	Anti-IL6	JAK Kinase Inhibitor
Route of Administration	SC/IV	SC/IV	Oral
ADRs	URTIs, Injection site reactions, influenza, cold sores	URTIs, injection site reactions, increased lipid parameters, increased liver enzymes, neutropenia	URTIs, headache, increased cholesterol levels, neutropenia, increased serum creatinine
Boxed Warnings	Serious infections, tuberculosis, fungal infections, opportunistic viral/bacterial infections, lymphoma	Serious infections, tuberculosis, fungal infections, opportunistic viral/bacterial infections, lymphoma	Serious infections, tuberculosis, fungal infections, opportunistic viral/bacterial infections, lymphoma

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