Adverse Effects of Pharmacotherapy Used in the Treatment of Rheumatoid Arthritis

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Jan. 2, 2014 (expires Jan. 2, 2017)
Activity Type: Knowledge-based
To earn continuing education credit:
ACPE Program 207-000-14-001-H01-P;
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Upon successful completion of this article, the pharmacist should be able to:

1. Describe the pathophysiology of rheumatoid arthritis.
2. Identify disease-modifying antirheumatic drugs (DMARD) and explain their mechanism of action or expected outcome in patients with rheumatoid arthritis.
3. Apply the mechanism of action of a given DMARD to anticipate its role in rheumatoid arthritis therapy and the associated adverse effects.
4. Contrast the roles of TNFα in rheumatoid arthritis and tuberculosis disease progression.
5. Identify the TNFα inhibitors and define the adverse effects associated with this class of agents.
6. Recognize the non-TNFα inhibitors and describe the adverse effects unique to each agent.

Upon successful completion of this article, the pharmacy technician should be able to:

1. Describe the basic pathophysiology of rheumatoid arthritis.
2. Identify disease-modifying antirheumatic drugs (DMARD) used in the treatment of rheumatoid arthritis.
3. Recognize the primary adverse effects associated with the DMARDs
4. Identify the biological agents (TNFα inhibitors and non- TNFα inhibitors) used in the treatment of rheumatoid arthritis.
5. Recognize the primary adverse effects associated with the biological treatment agents.

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INTRODUCTION

Rheumatoid arthritis (RA) is the most common autoimmune disease affecting the joints. It is estimated that approximately 1.3 million American adults are affected, with almost 75 percent of those being women. The international prevalence of rheumatoid arthritis is approximately 0.8 percent of the population. The incidence of RA increases with age and disease onset is highest between the fourth and sixth decades of life. In the United States, rheumatoid arthritis accounts for approximately 250,000 hospitalizations and 9 million office visits annually. It is estimated that the costs of arthritis and other rheumatological conditions was $128 billion in 2003, with $80.8 billion being accounted for by direct medical costs and $47 billion being attributed to indirect medical costs, such as lost wages. The treatment of RA has advanced significantly in recent years, thanks largely to the introduction of biological agents to the market, although disease-modifying antirheumatic drugs (DMARDs) are still highly effective for treatment. Despite their efficacy, drugs used in the treatment of RA can have serious adverse effects. Pharmacists are frequently involved in the direct care of patients with RA, both in the community and inpatient settings, and can therefore be of indispensable value in monitoring for these adverse effects.

REVIEW OF RHEUMATOID ARTHRITIS

Rheumatoid arthritis is an inflammatory disease that exerts its greatest impact on the synovial joints of the body. Typically, the smaller joints of the hands and feet are affected in a symmetrical pattern. The immune reactions result in increased blood flow to joints causing heat, redness, and swelling of the affected joints. Stretching of the pain receptors in the soft tissues and bone surrounding the joints causes pain. Prolonged, uninhibited inflammation of the synovial membrane will lead to accelerated degradation of the joint and, ultimately, a loss of joint function. Progressive joint damage and loss of joint function result in deformity and disability of the affected individual. Some resources report that more than a third of patients experience an inability to work due to RA related disability. This disability can occur soon after disease onset, with 80 percent of patients still working at two years and 68 percent of patients still in the workforce at five years.

Table 1. Extra-Articular Manifestations of Rheumatoid Arthritis

- Rheumatoid nodules (typically located on the exterior of the forearms)
- Hematologic effects: normocytic, normochromic anemia; thrombocytosis or thrombocytopenia; lymphadenopathy
- Felty syndrome—rheumatoid arthritis associated with splenomegaly and neutropenia
- Vasculitis which may involve the eyes, brain, skin, kidneys, heart, and gastrointestinal tract
- Pulmonary effects: pleural effusions, pulmonary nodules, interstitial lung disease
- Cardiovascular effects: pericardial effusions, valvular lesions
- Renal effects: microalbuminuria, mesangial glomerulonephritis
- Ophthalmologic effects: keratoconjunctivitis sicca; inflammation of the sclera, episclera, and cornea; Sjogren's syndrome
- Neurologic effects: mononeuritis multiplex and other effects caused by vasculitis
- Amyloidosis

The ill effects of rheumatoid arthritis extend beyond the joints and affect the entire body. High concentrations of inflammatory mediators in the body, such as tumor necrosis factor alpha (TNFα), interleukins, cytokines, and proteinases cause symptoms such as profound fatigue with unrelenting influenza-like symptoms, fever, sweating, and weight loss. Other systemic symptoms of rheumatoid arthritis include: dryness of the eyes and mouth (Sjogren's syndrome), nodules covering the extensions surfaces (such as backs of the elbows), fibrosis of the lungs, pleural and pericardial effusion, and vasculitis.

Patients with rheumatoid arthritis also have a higher incidence of ischemic heart disease and cardiac failure leading to premature death. The greatest risk of heart disease is present in patients with the most active RA due to circulating products of inflammation driving worsening atherosclerosis. There is also an increased incidence of osteoporosis and infection in these patients due to a combination of disease progression and treatment-related adverse effects. Patients with extra-articular disease and patients who develop serious adverse effects related to therapy (such as infection, tumors, and gastrointestinal toxicity) demonstrate a shortened life expectancy of three to five years. A more complete list of the extra-articular manifestations of RA is included in Table 1.

There is no definitive test for the diagnosis of rheumatoid arthritis. Therefore, the diagnosis is largely based on clinical signs and symptoms. The most commonly used classification criteria for rheumatoid arthritis are the American College of Rheumatology (ACR) 1987 revised criteria. According to these criteria, patients must meet at least four of the seven following criteria:

1) Morning stiffness in and around the joints lasting at least one hour
2) Soft tissue swelling or fluid in three or more joints simultaneously
3) At least one swollen joint in the hand
4) Symmetrical swelling of the joints
5) Rheumatoid nodules
6) Erosions or decalcification on x-rays of the hand and

Table 2. Poor Prognosis in Rheumatoid Arthritis

Presence of 1 or more of the following features:

- Functional limitation (such as Health Assessment Questionnaire-Disability index (HAQ-DI) or similar validation tool)
- Extra-articular disease (such as presence of rheumatoid nodules, RA vasculitis, Felty's syndrome)
- Positive rheumatoid factor or anti-cyclic citrullinated peptide antibodies
- Bony erosions by radiograph

wrists localized to or most significant adjacent to the involved joints

7) Abnormal serum rheumatoid factor

Morning stiffness and joint swelling must be present for a minimum of six weeks to be indicative of rheumatoid arthritis.

Laboratory tests recommended to assist in the diagnosis of rheumatoid arthritis include a complete blood count with differential, rheumatoid factor, and erythrocyte sedimentation rate (>30 mm/h) or C-reactive protein (>0.7 pg/ml). A positive rheumatoid factor is not diagnostic of RA because 20 percent of individuals with rheumatoid arthritis may never test positive for the rheumatoid factor, 5 to 10 percent of healthy individuals test positive for the rheumatoid factor, and the rheumatoid factor may be positive in individuals with other diseases. The likelihood of having a positive rheumatoid factor increases with duration of disease and age.

Other tests that are helpful for the diagnosis of rheumatoid arthritis include the anti-cyclic citrullinated peptide (anti-CCP) IgG antibody, arthrocentesis, and plain film radiography. The anti-CCP antibody is produced at the site of joint inflammation during first stage of rheumatoid arthritis. Its presence supports the diagnosis of rheumatoid arthritis and it is more than 98 percent specific when it is used in combination with the rheumatoid factor. However, anti-CCP antibodies are only present in about 60 percent of patients with rheumatoid arthritis. Arthrocentesis or joint aspiration is helpful when trying to rule out septic arthritis or a crystal-induced arthropathy. The synovial fluid can also be evaluated for the presence of anti-CCP antibodies. Plain film radiography can be used to determine the presence of bone and soft tissue changes. Renal and hepatic function tests are also recommended as part of the initial evaluation as this will help guide initial medication choices. It is also important to perform testing to rule out other diseases that are included in the differential diagnosis of rheumatoid arthritis. Diseases in the differential diagnosis include but are not limited to: connective tissue disease (such as systemic lupus erythematosus), fibromyalgia, other forms of arthritis (infectious, reactive, viral, osteoarthritis), sarcoidosis, acute rheumatic fever, crystalline arthropathy (such as polyarticular gout), and polymyalgia rheumatica.

Early diagnosis and prompt initiation of treatment reduces the progression of rheumatoid arthritis decreasing disability and disease burden. The disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and biological agents such as infliximab are the major drug classes used in the treatment of rheumatoid arthritis. The American College of Rheumatology recommendations use disease duration, disease activity, and the presence of features of poor prognosis to guide therapy initial therapy decisions with the goal of therapy being disease remission. Disease duration is defined as either early rheumatoid arthritis (fewer than six months) or established rheumatoid arthritis (six or more months, or meeting the 1987 ACR classification criteria). Disease activity is categorized as

Table 3. Early RA Therapy Recommendations

Low disease activity	DMARD monotherapy
Moderate/high disease activity without poor prognostic features	DMARD monotherapy OR Hydroxychloroquine + methotrexate
Moderate/high disease activity WITH poor prognostic features	DMARD combination therapy Double therapy Methotrexate + hydroxychloroquine Methotrexate + leflunomide Methotrexate + sulfasalazine Sulfasalazine + hydroxychloroquine Triple therapy Methotrexate + hydroxychloroquine + sulfasalazine
High disease activity WITH poor prognostic features	TNFα inhibitor with or without methotrexate EXCEPT infliximab which should be used in combination with methotrexate

low, moderate, high, or remission using validated scales. One such scale is the Simplified Disease Activity Index which uses number of swollen joints, number of tender joints, patient global score of disease activity, provider global score of disease activity, and C-reactive protein (CRP) to score disease activity as remission (≤3.3), low activity (>3.3 to ≤11), moderate activity (>11 to ≤26), and high activity (>26). Other validated scales include the Clinical Disease Activity Index, the Patient Activity Scale (PAS or PAS-II), the Routine Assessment of Patient Index Data 3, and the Disease Activity Score in 28 joints. Factors associated with a poor prognosis can be found in Table 2.

TREATMENT OF RHEUMATOID ARTHRITIS

For patients with early RA, the ACR guidelines recommend targeting low disease activity or remission as the treatment goals. Table 3 outlines the therapy recommendations for patients with early RA based on disease activity and presence of poor prognostic features.

For individuals with established RA, the ACR guidelines have recommendations for switching between and initiating additional therapies. Patients with disease deterioration after three months of DMARD monotherapy should have a second DMARD added to their regimen as long as poor prognostic features are not present. If patients receiving either methotrexate monotherapy or combination therapy with methotrexate and another DMARD continue to have moderate or high disease activity, another non-methotrexate DMARD should be added or the patient should be switched to another non-methotrexate DMARD. Alternatively, the ACR guidelines also state that these patients may be managed by adding on or switching to a TNFα inhibitor, abatacept, or rituximab. Switching to or adding on a TNFα inhibitor is recommended when patients still have moderate or high disease activity after three months of intensified DMARD combination therapy or after a second DMARD has been trialed.

In patients whose moderate or high disease activity persists after being treated for three months with a TNFα inhibitor, a switch to another TNFα inhibitor or use of a non-TNFα biologic is recommended if failure is due to a lack or loss of benefit. In patients treated with a non-TNFα biologic who still have moderate or high disease activity after six months a switch to another non-TNFα biologic or a TNFα inhibitor is warranted if the failure is due to lack or loss of benefit. The recommendation to wait six months to determine if a switch is warranted with non-TNFα biologic agents is due to the fact that a longer time may be required for these agents to demonstrate efficacy.

The ACR guidelines also provide guidance for changes in therapy for patients who experience adverse events while receiving treatment. The Food and Drug Administration (FDA) defines a serious adverse event as any event that is life threatening, causes initial or prolonged hospitalization, causes disability, or that requires an intervention to prevent permanent impairment or damage. Patients who experience a serious adverse event while receiving a TNFα inhibitor should be switched to a non-TNF biologic agent. In patients who experience a non-serious adverse event while receiving therapy with a TNFα inhibitor, a different TNFα inhibitor may be initiated or the patient may be switched to a non-TNFα biologic. Patients who experience any adverse event while receiving a non-TNFα biologic may be switched to another non-TNFα biologic or to a TNFα inhibitor.

The traditional DMARDs include hydroxychloroquine, leflunomide, methotrexate, sulfasalazine, minocycline, organic gold compounds, cyclosporine, and azathioprine. Due to a lack of new supporting literature, high incidence of adverse events, and/or infrequent use, azathioprine, organic gold compounds, and cyclosporine were not included in the 2008 ACR guidelines for the use of DMARDS and biologic agents or 2012 update to these guidelines. For this reason, azathioprine, organic gold compounds, and cyclosporine will not be discussed further.

Methotrexate

Methotrexate is a folate antagonist that is considered to be the cornerstone of rheumatoid arthritis therapy. It can be used alone or in combination with other DMARDs or the biological agents and is typically started first line for the treatment of rheumatoid arthritis. Methotrexate has been shown to not only improve the signs and symptoms of rheumatoid arthritis but to also decrease disease activity, inhibit radiographic progression, and prolong the life span of patients that are methotrexate responders. The anti-proliferative and immunosuppressive effects of methotrexate are thought to be due to a reduction of cell proliferation, an increase in apoptosis of T cells, an increase of endogenous adenosine release, an alteration of expression of cellular adhesion molecules, and an influence on production of cytokines, humoral responses, and bone formation. The benefits of therapy with methotrexate are generally seen within the first 6-8 weeks of therapy.

Methotrexate is generally well tolerated, with a favorable long-term adverse effect profile. Common adverse effects include nausea in relation to dose administration, oral ulceration, alopecia (reversible), rash, and an increase in the formation of rheumatoid nodules. A transient elevation of hepatic enzymes has been shown to occur in approximately 20 percent of patients but rarely requires discontinuation of therapy. Hepatoxicity may be more likely when methotrexate is concomitantly used with azathioprine, sulfasalazine, or leflunomide for combination therapy or with alcohol consumption. Myelosuppression can also be seen and can be increased with co-administration of trimethoprim-sulfamethoxazole. Pulmonary toxicities

including hypersensitivity pneumonitis (rare), interstitial fibrosis, pleuritis, pleural effusions, and pulmonary nodules may also be seen. Supplementation with folic acid can help lessen some of these adverse effects particularly the mucosal and gastrointestinal adverse effects. Hepatic adverse effects can also be lessened with folic acid supplementation. Folic acid supplementation has not been associated with a decrease in efficacy of methotrexate therapy.

The ACR guidelines recommend against initiating or resuming methotrexate in the presence of an active bacterial infection or a bacterial infection that is requiring antibiotic treatment, an active tuberculosis infection or a latent tuberculosis infection prior to starting preventive therapy, an active herpes zoster infection, or in the presence of an active, life-threatening fungal infection. Methotrexate is also contraindicated in patients with clinically important rheumatoid arthritis-associated pneumonitis or interstitial lung disease of unknown cause. Other contraindications to the use of methotrexate include a white blood cell count $<3000/mm^3$, a platelet count $<50,000/mm^3$, a history of myelodysplasia or if lymphoproliferative disorder had been diagnosed or treated in the last five years, and in the presence of acute hepatitis B or C. Additionally, methotrexate should not be initiated in women who are pregnant, planning to become pregnant, or breastfeeding.

Leflunomide

Leflunomide is an immune-modulator which inhibits replication of activated lymphocytes by blocking the de novo synthesis of pyrimidines and DNA. Through this action, leflunomide leads to a reduction in T-cell proliferation and auto-antibody production in B cells. Studies have shown leflunomide to improve HAQ scores and reduce radiographic progression of diseases, but to a lesser extent than methotrexate.

The most common adverse effects associated with leflunomide are gastrointestinal. Approximately 20 to 30 percent of patients experience nausea and diarrhea but these adverse effects may subside with continued treatment. Leflunomide has potential to cause hepatotoxicity and is therefore contraindicated in patients whose liver transaminases were greater than two times the upper limit of normal. When leflunomide is used in combination with methotrexate, the risk of hepatotoxicity increases significantly and can affect up to 60 percent of patients. Skin rash and alopecia (reversible) has been shown to occur in 5 to 10 percent of patients treated with leflunomide. Other adverse effects associated with the use of leflunomide include myelosuppression, infections, and new onset hypertension.

Similar to methotrexate, the ACR guidelines recommend against initiating or resuming leflunomide in the presence of an active bacterial infection or a bacterial infection that is requiring antibiotic treatment, an active tuberculosis infection or a latent tuberculosis infection prior to starting preventive therapy, an active herpes zoster infection, or in the presence of an active, life-threatening fungal infection. Use of leflunomide is also contraindicated in the presence of a white blood cell count $<3000/mm^3$, a platelet count $<50,000/mm^3$, a history of myelodysplasia or if lymphoproliferative disorder had been diagnosed or treated in the last five years, and in the presence of acute hepatitis B or C. In addition, leflunomide should not be initiated or resumed in women who are pregnant or planning a pregnancy or in women who are breastfeeding.

Hydroxychloroquine

Hydroxychloroquine is an antimalarial agent with immunomodulatory actions. It works by interfering with antigen presentation and the activation of the immune response by increasing pH within macrophage phagolysosomes. Hydroxychloroquine has an inhibitory effect on the production of pro-inflammatory cytokines such as interleukin(IL)-1, IL-6, and interferon-gamma. It has been proven to control the symptoms of rheumatoid arthritis; however, it has less effect on the inhibition of radiographic progression when used as monotherapy. Hydroxychloroquine is generally used in combination with a second DMARD. It is also one of the most well tolerated of the DMARDs. The most common adverse effects include the gastrointestinal toxicities (such as epigastric burning, nausea, bloating, diarrhea), skin rashes, and alopecia. An exacerbation of psoriasis can occur in patients using hydroxychloroquine. Hyperpigmentation of the skin in sun exposed areas may also occur. Rarely, patients may develop retinal toxicity with macular damage. Corneal deposits may occur in <0.1 percent of patients. Doses above 6 mg/kg/day are associated with an increased risk. This is reversible upon discontinuation of the medication.

Sulfasalazine

Sulfasalazine is cleaved in the liver to an anti-inflammatory agent (5-aminosalicylic acid) and an antibacterial agent (sulfapyridine). The exact mechanism of action in the treatment of RA is unknown. Similar to methotrexate, sulfasalazine inhibits folate-dependent enzymes causing impaired function of lymphocytes. Sulfasalazine also induces apoptosis of neutrophils and macrophages and this may contribute to its beneficial effects. Sulfasalazine has been shown to improve the signs and symptoms of rheumatoid arthritis and improve radiographic progression of the disease however it is not superior to other agents. Sulfasalazine is typically used in combination therapy with other DMARDs.

The most common adverse effects of sulfasalazine therapy include nausea, vomiting, loss of appetite, diarrhea, abdominal pain, skin rash, and pruritus. These effects occur in up to 30 percent of patients. Headache,

Table 4. Biological Agents Used in the Treatment of Rheumatoid Arthritis	
Agent	**Mechanism of Action**
Abatacept (Orencia)	Inhibits CD80/86 on T-cells
Adalimumab (Humira)	Tumor necrosis factor-α inhibitor
Certolizumab pegol (Cimzia)	Tumor necrosis factor-α inhibitor
Etanercept (Enbrel)	Tumor necrosis factor-α inhibitor
Golimumab (Simponi)	Tumor necrosis factor-α inhibitor
Infliximab (Remicade)	Tumor necrosis factor-α inhibitor
Rituximab (Rituxan)	Destroys B cells
Tocilizumab (Actemra)	Interleukin-6 antagonist

dizziness, and depression can also be seen. Oligospermia with impaired motility can occur in males but is usually reversed two to three months after discontinuation of sulfasalazine. Other, less common, adverse effects of therapy with sulfasalazine include leukopenia, myelosuppression, hemolytic anemia in patients with glucose-6-phosphate-dehydrogenase (G6PD) deficiency, transient elevation of hepatic transaminases, and hepatitis.

Sulfasalazine should not be used in patients with an aspirin or sulfa allergy or in patients with G6PD deficiency. Additionally, sulfasalazine initiation or resumption is contraindicated in the patients with a platelet count <50,000/mm^3. Sulfasalazine should not be initiated in patients whose hepatic transaminases are more than two times the upper limit of normal or in the presence of acute hepatitis, untreated chronic hepatitis B, and in treated or untreated chronic hepatitis C in patient with Child-Pugh class B and C liver disease. The ACR guidelines do not have a recommendation on the use of sulfasalazine in the face of renal dysfunction.

Minocycline

Minocycline is a tetracycline antibiotic generally only used as monotherapy in patients without poor prognostic features who have low disease activity and a short disease duration. Minocycline works in rheumatoid arthritis by inhibiting metalloproteinase-9 production, T-cell proliferation, and cytokine production. It is generally well tolerated. The most common adverse effects are nausea, vomiting, and diarrhea. Skin hyperpigmentation and photosensitivity reactions are less common but can occur. Also in the literature are reports of autoimmune induction including a lupus-like syndrome and an anti-neutrophil cytoplasmic antibody-positive vasculitis.

According to the ACR guidelines, contraindications to the use of minocycline include acute hepatitis, treated chronic hepatitis B and hepatitis C for Child-Pugh class C, and untreated chronic hepatitis B and hepatitis C for all Child-Pugh classes. Minocycline is also contraindicated for use in women who are pregnant or planning to become pregnant and in nursing mothers.

BIOLOGIC AGENTS

The use of biologic agents in the treatment of rheumatoid arthritis has increased dramatically over the last 10 years. Biologic agents can be broadly defined as diagnostic or treatment agents derived from living organisms. In 2012, the ACR updated their guidelines on the management of RA from 2008, in part due to the growing amount of literature on using biologic agents in the last few years as well as the number of agents that have been introduced to the market. Biological agents have a number of potential advantages to traditional DMARDs, particularly the fact that biological agents can target specific immune mediators, theoretically making them both more effective and safer than traditionally used agents. However, because these agents are immune modulators, there are important safety concerns that must be carefully examined prior to use. One of the most publicized adverse effects of biological agents is the propensity to increase the risk of developing infections, particularly tuberculosis (TB) and other bacterial infections, as well as certain fungal infections. Additionally, biological agents may place patients at an increased risk of developing cancer, heart failure, lupus-like syndromes, and neuronal demyelination. However, it is difficult to separate the true incidence of biological agents causing these disorders as it is known that patients who have RA are already at an increased risk of developing infections, cancer, and cardiovascular disease. Much of the literature examining these adverse effects—particularly the infectious complications—are in the form of case reports or small studies.

The most likely reason for this is that these particular adverse effects are uncommon, and most pre-marketing trials typically do not include a sufficient number of patients to properly detect the uncommon adverse effects of drugs. The following sections will carefully examine the biological agents used in the treatment of RA with a special focus on the adverse effects associated with each agent.

TNFα Inhibitors

Biological agents used in the treatment of RA can be generally divided into two groups: TNFα inhibitors and non-TNFα agents. Table 4 lists the currently available biological agents used in the treatment of RA as well as their specific mechanisms of action. TNFα inhibitors were the first biological agents to come to the market for the treatment of RA and have since become a mainstay of treatment. To understand how these agents work, it is important to first have an understanding of the role that

TNFα normally plays in the body. TNFα is a cytokine that is heavily involved in the body's response to infection and inflammation through a variety of mechanisms. It assists in the production of other cytokines involved in inflammation and activates adhesion molecules which promote cells to travel into sites of inflammation. Because of TNFα's role in the mediation of inflammation, it consequently plays an important role in the pathophysiology of RA. In fact, it is commonly found in the synovial fluid of patients with RA. There are currently five TNFα-inhibitors marketed for the treatment of RA: adalimumab (Humira), etanercept (Enbrel), infliximab (Remicade), certolizumab pegol (Cimzia), and golimumab (Simponi).

As a class, the TNFα inhibitors are generally well tolerated by patients. There are some common adverse effects that can be seen across this class of agents. All of the currently available TNFα inhibitors are only available parenterally, either via intravenous infusion in the case infliximab or by subcutaneous injection for the remaining four agents. Due to the parenteral route of administration, all TNFα inhibitors can be associated with acute infusion reactions (AIRs) and injection site reactions (ISRs). Of note, anaphylactic reactions can occur with any of these agents, though this seems to be an uncommon manifestation of AIRs. Other commonly associated adverse effects include nausea, headache, and upper respiratory tract infections (URTIs).

TNFα-inhibitors and Tuberculosis Infections

As mentioned previously, one of the most serious and widely publicized adverse effects of TNFα inhibitors is their association with the reactivation of *Mycobacterium tuberculosis* infections. A common misconception among both the public at large as well as clinicians is that TNFα inhibitors actually cause patients to become infected with TB. However, it is more accurate to say that treatment with TNFα inhibitors leads to the reactivation of latent TB infections in those who have already been exposed. They may also possibly increase the likelihood of becoming infected if exposed to TB after treatment with TNFα inhibitors has been initiated, as will be described as follows.

Tuberculosis remains a global problem, with more than 8 million new cases diagnosed annually. Some authorities estimate that TB infects as much as one-third of the world's population, and it has a high association with concomitant HIV infection. Unlike many other infectious organisms, *Mycobacterium tuberculosis* often does not initially cause clinical infection, and many individuals may not realize that they have even been exposed. Approximately 2 million people die annually from TB, although the number may vary considerably from year to year. If left untreated, as many as one third of individuals die within the first year, and half die within five years.

Clinical infection with TB depends largely on host immune factors. For individuals with a competent immune system, the initial response to TB exposure is the ingestion of the bacteria by pulmonary macrophages. TNFα, in addition to the bodily roles described above, is also involved in the activation of macrophages directed against TB. It also plays an important role in granuloma formation. Granulomas are formed by macrophages and lymphocytes and are formed to contain microorganisms and thus prevent dissemination of infections. This granuloma formation is particularly important in the host defense against TB and is a classic feature following TB exposure. Thus, TNFα is involved in both the acute response after initial TB exposure through macrophage activation as well as in the later stages after exposure by helping to maintain granuloma integrity. If TNFα is inhibited with drug therapy, it is not available to help in the activation of macrophages in response to TB exposure. Further, the lack of TNFα can lead to loss of granuloma integrity, which can subsequently cause the activation of latent TB. This has been demonstrated repeatedly in animal models.

The exact incidence of the association between TNFα inhibitors and TB infections is very difficult to estimate. It appears to be an uncommon occurrence, given that it was not seen in pre-licensure trials for any of these agents. There are additionally many confounding variables in relation to the reports regarding this unusual adverse effect. As mentioned previously, it is already known that patients with RA are at an increased risk of infectious complications, including TB, due to the disease process. Also, many patients who receive TNFα inhibitors are also receiving

Table 5. CDC-defined Risk Factors for TB Infections

- Close contact with persons known or suspected to have active TB infection
- Foreign-born persons who have lived in areas with a high incidence of TB (Africa, Asia, Eastern Europe, Latin America, or Russia)
- Contact with persons who visit areas with a high incidence of TB, particularly if the visits occur often or are prolonged
- Residents and employees of places where persons are at high risk for TB (prisons, long-term care facilities, and homeless shelters)
- Health care workers exposed to patients at high risk of developing TB
- Locally defined populations that have an increased risk for developing TB (medically underserved, low income populations, or abusers or drugs/alcohol
- Infants, children, and adolescents exposed to adults at an increased risk for developing TB

**Adapted from the ACR 2012 update on drug therapy for rheumatoid arthritis*

Table 6. Bacteria and Fungi Associated With Treatment With TNFα Inhibitors

Bacteria	Fungi
Streptococcus pneumonia	*Histoplasma capsulatum*
Staphylococcus aureus	*Pneumocystis jirovecii*
Streptococcus pyogenes	*Coccidioides immitis*
Nocardia species	*Cryptococcus neoformans*
Salmonella species	*Candida* species
Brucella species	*Aspergillus* species
Bartonella species	
Listeria monocytogenes	Other—Toxoplasma species (protozoa)

other immunosuppressive medications, such as methotrexate and corticosteroids, making it difficult to elucidate the true incidence for the individual agents. However, based on the availability of published data, the prevalence of TB associated with TNFα inhibitors does appear to be higher than the prevalence in both the general population and the RA population. This is particularly true for infliximab. However, as infliximab was the first TNFα inhibitor to come into widespread use, there will naturally be more data associated with it, so this may not necessarily mean that it truly is associated with a higher incidence compared with the other TNFα inhibitors. It has been shown that TB infection is much more likely to occur during the first two years of therapy with TNFα inhibitors, making early cognizance of this adverse effect pivotal for the clinician.

The 2012 ACR guidelines make specific recommendations for TB screening in all patients who are candidates for biological therapy. These guidelines recommend that all patients who are being considered for therapy with biological agents to be screened for TB, regardless of their risk factors for infection. However, the clinician should assess the patient's medical history for the presence of risk factors (see Table 5). The initial screening may be done with the tuberculin skin test (TST) or interferon-γ-release assays (IGRAs). An IGRA screen is preferred in all individuals who have the Bacillus Calmette-Guérin (BCG) vaccine due to the high likelihood of false positive TSTs in this population. The BCG vaccine is a vaccine against TB that is used in countries outside of the United States. All patients with a positive initial or repeat TST or IGRA should undergo chest radiography. If this suggests active TB, a sputum culture should be performed.

It is important to note that RA patients may experience a false-negative TST or IGRA due to immunosuppression. Therefore, if the patient has risk factors, or there is clinical suspicion of TB, a repeat test should be considered one to three weeks after the initial screening. A list of the Centers for Disease Control (CDC) defined risk factors for TB infections is provided in Table 5. If a patient initially tests negative and no risk factors or clinical suspicion is present, further work-up for TB is likely unnecessary, and patients may begin treatment with a TNFα inhibitor. If the patient is found to have active or latent TB, appropriate antimicrobial therapy and referral to a TB specialist should occur immediately. It should also be noted that infection with TB does not necessarily mean that treatment with TNFα inhibitors or any other biological is completely contraindicated. If a patient has latent TB, treatment with a biological agent may be initiated or resumed after one month of therapy with antitubercular pharmacotherapy has been completed. If the patient has active TB, biological treatment can be initiated or resumed once a full treatment course against active TB has been completed. Patients who are exposed to TB after biological treatment has started, or who are likely to experience exposure, should have repeat TB testing performed at least annually.

TNFα inhibitors and Other Bacterial Infections

Although the association between TNFα inhibitors and TB has received much attention in both the media and the medical literature, these agents are also associated with other, more common bacterial infections. Table 6 lists some of the more common bacteria that have been associated with TNFα inhibitor treatment. These bacteria can cause a wide range of clinical syndromes, including severe sepsis, septic arthritis, pneumonia, bronchitis/sinusitis, bursitis, peritonitis, and pyelonephritis. Of particular interest, the opportunistic bacteria *Listeria monocytogenes* has been associated with treatment with TNFα inhibitors.

Although not a commonly encountered pathogen in any population, *Listeria monocytogenes* has been known to cause infections in neonates, pregnant women, and immunocompromised patients in general. Studies in animals have suggested that TNFα may be involved in host defense mechanisms against this pathogen, so inhibition would likely predispose to infection. Much like TB, it appears to be an uncommon source of infection, though numerous case reports have been noted in association with TNFα inhibitors. Some of these cases report very serious infections, such as sepsis and meningitis. In fact, several cases report patient mortality in association with *Listeria* sepsis.

It should be noted that the vast majority of patients in these case reports were elderly (older than 60 years of age) or receiving other immunosuppressive therapy, making them already at risk for *Listeria* infection, and thus making the true incidence of infection associated with TNFα inhibitor therapy difficult. Patients who are on TNFα inhibitors should be counseled to avoid potential sources of *Listeria*, such as unpasteurized dairy products, and to heat (until steaming) ready-to-eat food products such as hot dogs.

TNFα Inhibitors and Fungal Infections

Post-marketing surveillance reports have demonstrated that treatment with TNFα inhibitors may predispose patients to opportunistic fungal infections with different species of both yeasts and molds. Table 6 lists some specific fungal species that have been reported following treatment with TNFα inhibitors. As with the other infections described previously, the available data for the risk of fungal infections is derived from case reports or small case series. Patients who have generalized immune suppression are known to be at an increased risk for developing fungal infections. However, incidence rates specific to patients with RA have not been elucidated. Therefore, it is difficult to determine if RA patients are already at an increased risk for the development of these fungal infections, or if TNFα inhibitor therapy is the contributing factor. Interestingly, it is currently known that TNFα is involved in recruiting neutrophils into the lungs when infected with fungi such as *Cryptococcus neoformans* and the *Aspergillus* species, which helps explain why inhibition of TNFα might predispose to infections with these organisms.

Perhaps the most widely reported fungal infections connected to TNFα inhibitors are with *Histoplasma capsulatum* and *Pneumocystis jirovecii*. *Pneumocystis jirovecii* is a common opportunistic pathogen in patients with underlying immunosuppression, particularly oncologic disorders and HIV. TNFα is known to be involved in host defenses against *Pneumocystis jirovecii* infections. With regard specifically to infection with *Histoplasma capsulatum*, the case reports show that the patients infected were already living in areas endemic to *Histoplasma* and were also receiving other immunosuppressive medical therapies. Patients who are living in *Histoplasma* endemic areas must carefully weigh the benefits versus risks of TNFα inhibitor therapy prior to beginning treatment. Additionally, patients on therapy should avoid any activity that would increase the risk of *Histoplasma* infection. This would include avoiding cleaning chicken coups, cave exploration, and disturbing the soil beneath areas of bird-roosting.

Other Complications of TNFα Inhibitor Therapy

TNFα inhibitors can potentially cause a wide array of adverse effects aside from the infectious complications described previously. A particularly worrisome potential adverse effect is the development of oncologic disorders, specifically lymphoma. This particular adverse effect of the TNFα inhibitors is extremely difficult to define in patients with RA, even more so than the infectious complications, because there was already a well-defined increase in the incidence of lymphoma in patients who have RA, even prior to the introduction of the TNFα inhibitors to the market. In fact, some studies suggest that the TNFα inhibitors do not increase the risk of developing lymphoma to any greater extent than the incidence seen in the general population.

However, other studies detect a subtle increase in the risk of lymphoma associated with TNFα inhibitors. Certain features of some of the cases reported in the literature do heighten the increased concern. For example, in a majority of the cases, the diagnosis of lymphoma was made within eight weeks of beginning therapy with a TNFα inhibitor. Additionally, some cases of lymphoma that had been in remission reoccurred after starting TNFα inhibitor therapy. Although the data regarding the incidence of lymphoma is unclear at this time, clinicians should be cognizant of this possible association.

TNFα inhibitors have also been implicated in either inducing new onset heart failure or worsening already existing heart failure. These agents should generally not be utilized in patients who have class III/IV heart failure. Based on published reports, it appears that worsening heart failure in patients already diagnosed is more common than the induction of new onset heart failure. Although a small number of cases have been reported that identify new onset heart failure, the association is not clear at this time. Interestingly, patients with heart failure are often shown to have increased TNFα levels, suggesting that this might be an area for potential treatment of heart failure. However, this does not seem to hold true based on the currently available evidence.

There are two additional rare adverse effects of TNFα inhibitors that clinicians should be aware of: development of demyelinating disease and systemic lupus erythematosus-like syndromes. Cases of demyelinating disease have been reported only rarely, and a direct cause from TNFα inhibitors cannot be adequately established from the reports. However, extreme caution should be exercised if patients at increased risk of demyelinating diseases are being considered for therapy with TNFα inhibitors. Systemic lupus erythematosus-like syndromes appear to generally be reversible upon discontinuation of the offending TNFα inhibitor.

Non-TNFα Inhibitors

There are currently three biologic agents available on the market possessing a different mechanism of action than inhibition of TNFα: abatacept (Orencia), rituximab (Rituxan), and tocilizumab (Actemra). Abatacept and tocilizumab are available in both intravenous and subcutaneous formulation, while rituximab is only available intravenously. While some adverse effects of these agents overlap with those of the TNFα inhibitors, these agents generally have adverse effect profiles unique to each individual agent. The non-TNFα agents are associated with frequent adverse effects, in some cases as high as 96 percent. However, adverse effects are usually mild or moderate and seldom require the discontinuation of treatment. Like the TNFα inhibitors, all of these drugs can

cause infusion reactions such as nausea, vomiting, and headache. Infections are commonly reported, and the overall incidence of infection can be quite high, with more than half of patients experiencing some type of infection. Although this seems like an alarmingly high number, it should be noted that most cases of infection appear to be mild, such as upper respiratory infections. We will review the unique adverse effects associated with each of these agents in the following paragraphs.

Abatacept (Orencia) is a selective costimulation modulator. Under normal conditions, antigen-presenting cell protein CD80/86 interacts with CD28 and together they stimulate activation of T lymphocytes, which results in the release of inflammatory cytokines in RA. Abatacept binds to CD80/86, preventing it from interacting with CD28 resulting in less T lymphocyte activation. The biologic classification comes from the protein, cytotoxic T lymphocyte-associated (CTLA)-4 which inhibits T-cell activation by binding to CD80/86, rendering it unable to bind to CD28. Abatacept is a formulated CTLA-4 protein, which works to decrease the inflammatory response in RA. It is indicated for moderately to severely active RA as monotherapy or in combination with a DMARD other than a TNFα inhibitor. Therapy is initiated with a 30-minute intravenous infusion after which the drug may be administered intravenously every four weeks or subcutaneously once weekly.

An increase in the incidence of TB has thus far not been noted with the use of abatacept, though routine screening is still recommended as described above. However, serious infections other than TB have been reported, with mortality noted in some situations. The most common serious infections reported include pneumonia, urinary tract infections, and gastroenteritis, although severe sepsis has also been reported. The risk of malignancies is a concern with any biological agent, but based on the available evidence it appears that abatacept does not present any higher risk when compared to traditional DMARDs.

Rituximab (Rituxan) is a chimeric human monoclonal antibody directed against the CD20 protein expressed on pre-B cells and mature B cells. It depletes B cells by inducing apoptosis, complement activation, and cytotoxicity. Rituximab is indicated to be used in combination with methotrexate for patients who have inadequately responded to a TNFα inhibitor. The most common adverse effect reported with rituximab is infusion reactions, which are characterized by itching, fever, rash, chills, bronchospasms, hypotension, and angioedema (swelling of the hands, feet, and face). It carries a black box warning for fatal infusion reactions, severe mucocutaneous reactions, hepatitis β virus reactivation and progressive multifocal leukoencephalopathy.

Severe infusion reactions include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death. Pre-treatment with acetaminophen and an anti-histamine is recommended. Glucocorticoid administration (such as methylprednisolone 100 mg IV) 30 minutes prior to infusion of rituximab is recommended for RA patients.

Rituximab is also notable in that it is associated with the reactivation or exacerbation of viral infections, particularly hepatitis B virus (HBV). Screening is therefore recommended in patients who are at risk for HBV infection, and treatment should be considered for HBV carriers prior to therapy with rituximab. Increased incidences of malignancies and TB have not been noted with rituximab treatment. However, there have been case reports of progressive multifocal leukoencephalopathy (PML) after treatment with rituximab. Most patients in these reports had underlying malignancies, such as lymphoma, or had undergone stem cell transplantation. Caution should be exercised in these patients if rituximab therapy is to be considered.

Tocilizumab (Actemra) is a recombinant monoclonal antibody directed against the human IL-6 receptor. Under normal conditions, IL-6 binds to membrane-bound or soluble IL-6 receptors, which in turn binds to the 130 gp signal transducer. This causes angiogenesis and increases the activity of adhesion molecules, resulting in an overall increase in the inflammatory process. Additionally, IL-6 activates both T and B helper cells. Tocilizumab works to block IL-6, thus causing a pronounced decrease in the inflammatory cascade. It is indicated for monotherapy or in combination with methotrexate and other non-biologic DMARDs and is administered as an intravenous infusion every four weeks or once-weekly subcutaneous injection. Tocilizumab carries a black box warning for severe infections that may lead to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections.

Tocilizumab appears to be overall well-tolerated, with fewer associated adverse drug events compared to other biologic agents. Infectious complications appear to be the most common adverse effect, and may range from mild infections such as nasopharyngitis to much more severe infections such as pneumonia and gastroenteritis. It does not appear to cause in increase in HBV infection or malignancies. Tocilizumab can cause an increase in liver function tests, so it is recommended that these be monitored at baseline and then periodically. Although uncommon, it can cause a pronounced decrease in neutrophil counts, though this was reversible upon discontinuation of the drug. There have additionally been reports of gastrointestinal perforation, so extreme caution should be used in patients who have a history of diverticulitis or intestinal ulceration. Lastly, tocilizumab can increase total, LDL, HDL, and triglyceride levels, though this tends to stabilize with continued treatment.

CONCLUSION

Rheumatoid arthritis is a cause of significant morbidity in the American population. Although DMARDs are still the drugs of choice in many patients with RA, the advent of biological agents in recent years has caused a paradigm shift in the treatment of this disorder. The pharmacotherapeutic options for the treatment of RA have a significant impact on disease progression. Despite their high efficacy, these agents are all associated with significant adverse effects, and careful monitoring of patients is of utmost importance. Because of their expertise on medication therapy and easy access to patients, pharmacists are in the unique position to not only counsel patients on their pharmacotherapy, but also help monitor for these adverse effects. ■

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Continuing Education Quiz

Select the correct answer.

Use the following case to answer questions 1-7.

JK is a 65-year-old female with a two-month history of morning stiffness and swollen joints of the hands. Physical examination reveals nodules on the elbows. The physician orders a complete blood count (CBC) with differential, rheumatoid factor, erythrocyte sedimentation rate (ESR), and an X-rays of the hand and wrist. The CBC shows a normocytic, normochromic anemia. The ESR was elevated but the rheumatoid factor is negative. The X-rays show some decalcification of the joints of the hand. Despite the negative rheumatoid factor, the physician diagnoses JK with rheumatoid arthritis.

1. The physician would like help determining an appropriate initial treatment for JK. According to the American College of Rheumatology guidelines, what information would be needed to determine an initial treatment regimen for JK?
a. Presence of poor prognostic factors
b. Disease activity score
c. Duration of disease
d. All of the above

2. Using the Simplified Disease Activity Index, JK is found to have a disease activity score of 24. Which disease activity category is JK?
a. Low activity
b. Moderate activity
c. High activity
d. Remission

3. Which regimen is most appropriate for JK at this time?
a. Methotrexate monotherapy
b. Hydroxychloroquine monotherapy
c. Methotrexate + Minocycline
d. Methotrexate + Leflunomide

4. Which of the following are benefits of therapy with methotrexate?
a. Methotrexate inhibits radiographic progression of rheumatoid arthritis.
b. Methotrexate has no effect on the life span of methotrexate responders.
c. Methotrexate increases disease activity scores.
d. All of the above

5. JK is concerned about adverse effects with the use of methotrexate. Which statement about the use of methotrexate is TRUE?
a. Methotrexate use is associated with a transient elevation of hepatic enzymes.
b. Methotrexate causes a transient decrease in glomerular filtration rate.
c. Methotrexate has no gastrointestinal symptoms.
d. Hypersensitivity pneumonitis is a common adverse effect with the use of methotrexate.

6. Folic acid supplementation can decrease the gastrointestinal symptoms of methotrexate use but will have no effect on the hepatic toxicity.
a. True
b. False

7. Hepatotoxicity with methotrexate may be more likely when used concomitantly with which of the following?
a. Leflunomide
b. Alcohol
c. Sulfasalazine
d. All of the above

Use the following case to answer questions 8-11.

DS is a 44-year-old male with a one-year history of rheumatoid arthritis. He has been treated with methotrexate monotherapy but has experienced an increase in disease activity. DS does not have poor prognostic features.

8. What is an appropriate therapeutic option for DS to reach remission?
a. Have DS start taking ibuprofen for pain.
b. Add on a second DMARD
c. Discontinue methotrexate and begin monotherapy with minocycline.
d. None of the above

9. After doing his own internet research, DS would like to know about the adverse effects of sulfasalazine. Which of the following statements about sulfasalazine is true?
a. Less than 3 percent of patients taking sulfasalazine experience symptoms of nausea, vomiting, or loss of appetite.
b. Oligospermia is a common, irreversible adverse effect of sulfasalazine therapy.
c. Sulfasalazine can be associated with skin rash and pruritis.
d. None of the above are associated with sulfasalazine therapy.

10. While on vacation with his wife, DS begins to feel ill and has to be taken to the hospital. Within 24 hours, blood cultures are positive for methicillin resistant *Staphylococcus aureus* and DS is started on vancomycin 1 gram IV every 12 hours. When filling out the medication reconciliation form for DS, the physician continues the methotrexate and sulfasalazine. Which of these is the most appropriate intervention for a pharmacist to make?
a. No intervention is needed. According to the ACR guidelines, both sulfasalazine and methotrexate can be used in the presence of an active bacterial infection.
b. According to the ACR guidelines, both methotrexate and sulfasalazine are contraindicated in the presence of an active bacterial infection.
c. According to the ACR guidelines, methotrexate should not be continued while patients are receiving treatment for a bacterial infection.
d. According to the ACR guidelines, sulfasalazine should not be continued while patients are receiving treatment for a bacterial infection.

11. Sulfasalazine should not be initiated in patients with acute hepatitis but may be started in the presence of chronic hepatitis regardless of type and Child-Pugh score.
a. True
b. False

Use the following case to answer questions 12-15.

RT is a 55-year-old white female with a history of rheumatoid arthritis, previously treated with methotrexate. She has progressed to high disease activity and her rheumatologist wishes to begin therapy with a biological agent, preferably with a TNFa inhibitor, and wishes to get input from the pharmacist. Her past medical history is significant for dyslipidemia and hypertension. She lives with her husband on a chicken farm and has one son and one daughter.

12. If taking into account her rheumatologist's preferences, which of the following would be the best option for RT at this time?
a. Abatacept
b. Etanercept
c. Rituximab
d. Tocilizumab

13. Which of the following adverse effects could potentially be caused by the biological agent that you elect to initiate in RT?
a. Tuberculosis
b. *Pneumocystis jirovecii* pneumonia
c. Heart failure exacerbations
d. All of the above

14. TNFα is a cytokine involved in the body's response to inflammation by assisting in the production of other cytokines involved in inflammation and by activating adhesion molecules which promote cells to travel into sites of inflammation.
a. True
b. False

15. Based on RT's past medical and social history, which of the following pathogens would she likely be at most risk for acquiring if she were to begin therapy with a TNFα inhibitor?
a. *Listeria monocytogenes*
b. *Streptococcus pyogenes*
c. *Nocardia* species
d. *Histoplasma capsulatum*

Use the following case to answer questions 16-19.

JA is a 63-year-old African American male who is being evaluated for rheumatoid arthritis. After his evaluation, he is found to have high disease activity, with a positive rheumatoid factor and extra-articular disease. He has a past medical history of type 2 diabetes mellitus and hypertension.

16. Only patients who are to undergo therapy with TNFα inhibitors must be screened for tuberculosis prior to initiation of treatment.
a. True
b. False

17. JA's physician wishes to begin treatment with methotrexate and infliximab. He has an initial TB screen with a skin test, which was positive. Which of the following would be the next most appropriate initial step for this patient?
a. Obtain a sputum culture.
b. Begin treatment with methotrexate and infliximab.
c. Perform chest radiography
d. Begin treatment with a non-TNFa inhibitor

18. JA is found to have active TB after an appropriate work up and treatment has been initiated. Because of his severe RA, the physician still wishes to begin treatment with a biological but asks for your opinion. Which of the following would be the best response to the physician?
a. JA may begin biological therapy one month after starting treatment for the active TB.
b. JA may begin biological therapy six months after starting treatment for the active TB.
c. JA may begin biological therapy immediately after starting treatment for the active TB.
d. JA may begin biological therapy after a full treatment course for the active TB has been completed.

19. Which of the following individuals would be at highest risk of developing TB infection?
a. The nurse taking care of a patient on therapy with methotrexate
b. The physician who sees patients at a local nursing home
c. The pharmacist who counsels a patient being treated with golimumab
d. The patient using the same outpatient infusion center as patients being treated with TNFa inhibitors

20. Which of the following laboratory tests should be monitored in patients taking tocilizumab?
a. Cholesterol levels
b. Liver function tests
c. Complete blood counts
d. All of these should be monitored