IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
May 2020 Vol.:18, Issue:2

A Review on Side Effects Associated with Disease Modifying Anti Rheumatism Drugs in Rheumatoid Arthritis Patients

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

CHHAYA CHAUHAN *, VIJENDER SINGH, HEMA ARYA, VANDANA

School of Pharmacy
Sharda University
Greater Noida, 201306- U.P. India.

Submission: 23 April 2020
Accepted: 30 April 2020
Published: 30 May 2020

Keywords: Biologic DMARDs, non- biologic DMARDs, Synthetic DMARDs, Non-synthetic DMARDs, autoimmune, synovial joints

ABSTRACT

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that involves inflammation of synovial joints that causes progressive articular damage, functional loss, and co-morbidity. Rheumatoid arthritis is the most commonly diagnosed systemic inflammatory disease, with a lifetime prevalence of up to 1% worldwide. Both genetic and environmental factors are responsible for the development of Rheumatoid arthritis. Diagnosis involves a positive test for HLA-DR beta and rheumatoid factor. Patients with a high risk of developing RA have a high number of inflamed joints and high ESR (Erythrocyte sedimentation rate). Disease Modifying Anti Rheumatic Drugs (DMARDs) are considered as first-line treatment for rheumatoid arthritis. Treatment with Biologic or Non- synthetic DMARDs and non- biologic DMARDs or Synthetic DMARDs associated with several potential side effects and these should be closely observed during the overall treatment. Biologic DMARDs include Etanercept, Infliximab, Adalimumab, Golimumab, and Certolizumab, etc. Synthetic DMARDs include Methotrexate, Leflunomide, Hydroxychloroquine (HCQ) and Sulfasalazine, etc. Treatment of Rheumatoid Arthritis with Biologic DMARDs associated with risk of tuberculosis, heart attack, cardiovascular diseases, hepatitis, and susceptibility towards various infections. Non-biologic DMARDs causing side effects associated with gastrointestinal tract, central nervous system, hypertension, and hematological abnormalities.Keeping in mind the side effects associated with treatment with Biologic DMARDs all the patients must be screened for any infection, including Tuberculosis and Hepatitis. On developing any serious infection treatment should be discontinued and restarted once the infection gets resolved. Synthetic DMARDs requires monitoring of blood and development of any potential side effects.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation of the synovial joints which leads to the progressive destruction of the bone [1,2]. It may also affect many tissues and organs, including blood vessels, heart, skin, lungs, and muscles. The onset and severity of the disease are variable and usually insidious. RA initially presents with fatigue, musculoskeletal pain, and stiffness, and only after weeks to months does it progress to involve joints. Generally, the small joints are affected first, particularly the small bones of the hands. Later larger joints are affected, becoming swollen, warm, and painful [3]. Human life is not possible when the movement of the joints challenged and the cytokines are responsible for the inflammation in the joints[4]. RA is a more widespread disease and its presence caused a sharp degrade in the physical and mental health of the people. About 1 percent of the American population lives with rheumatoid arthritis[5]. According to a 2017 report in the journal *Rheumatoid International*, the prevalence of RA in the United States increased between 2004 and 2014, affecting about 1.3 million adults in 2014[6].

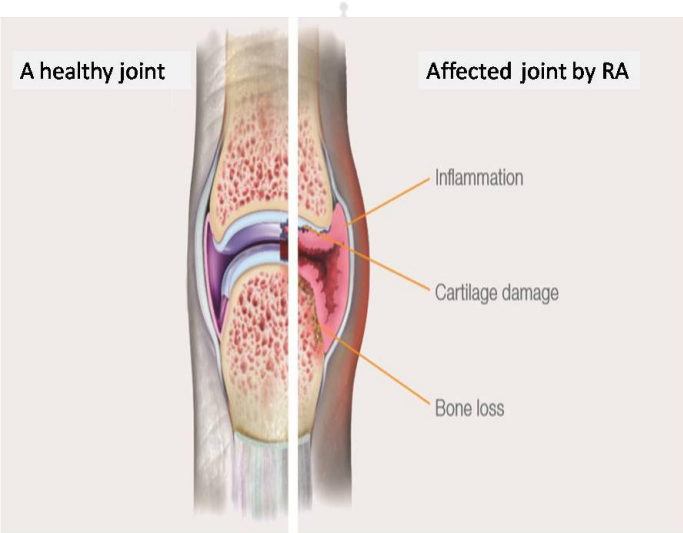

Figure No. 1: Affected and normal sides of a human joint

This disease can affect at any age of the people but people particularly women with the age of 40 to 70 years are more prone to rheumatoid arthritis[7].RA is typically characterized by morning stiffness and symmetrical joint swelling of the feet, hands, and knees, although any joint (and in some cases, internal organs) may be involved[7]. RA is considered a clinical syndrome that encompasses several disease subsets, each of which involves a distinct inflammatory cascade that can lead to joint damage, deformity, and organ dysfunction[8]. The

course of RA may be complicated by cardiac, hematologic, and other extra-articular manifestations[7].

Early signs of disease, such as joint swelling, joint pain, and joint stiffness, typically begin gradually and subtly, with symptoms slowly developing over weeks to months and getting worse over time. RA usually begins in the small bones of the hands and wrists. When left untreated, inflammation can start to develop in other parts of the body, causing various potentially serious complications that can affect other organs, such as the heart, lungs, and nerves, and could cause significant long-term disability. If someone is experiencing RA symptoms, it's crucial to get diagnosed as soon as possible to receive prompt treatment. Historically, RA was associated with both progressive disability and a shortened lifespan, although improvements in diagnosis, as well as aggressive use of both non-biologic and biologic disease-modifying anti-rheumatic drugs (DMARDs), have greatly improved prognosis in the past 20 years[9].

DMARDs work by slowing the inflammation and protecting the joints from further damage. These drugs are generally prescribed shortly after diagnosis. The type of DMARD a doctor prescribes depends on several factors, including disease severity and the balance between the medication's benefits and potential side effects. Frequent use of disease-modifying anti-rheumatic drugs should be monitored very carefully otherwise adverse drug reactions and their incidence brings health hazard or side effect.

Epidemiology

Rheumatoid arthritis affects about 1% of the world's population with relatively low variation in incidence among countries[3]. Annually, the incidence of RA is 30 per 100,000 people[10]. When matched for age, 2–3 times more women are affected with RA than men. The prevalence of RA increases with age in both sexes and is greatest in patients aged 40–70 years[7]. Heritability analysis and genetic markers suggest a genetic link to RA. The cause of RA remains to be fully elucidated but likely involves both genetic and environmental factors. In a joint affected with RA, there is chronic pain and inflammation of the synovial tissue lining the joint capsule. In RA various proteins get modified and begin the inflammatory process by acting as autoantigens[11]. The inflammatory process involves stimulation of T lymphocytes and B cells and, ultimately, the formation of autoantibodies by way of plasma cells. Autoantibodies such as rheumatoid factor and anti-citrullinated protein antibodies

(ACPAs) may be detected before the clinical disease is apparent. Rheumatoid factor is generally a polyclonal immunoglobulin (Ig) M antibody and is present in 85%– 90% of patients. Although not specific to RA, higher levels of rheumatoid factor are associated with more severe RA. Inflammation of the synovium results in tissue proliferation (referred to as pannus) and may lead to an invasion of cartilage and erosion of bone. The progression of the disease is variable for each patient but is usually insidious versus abrupt. Patients at risk of developing joint abnormalities or disability include those with a high number of inflamed joints, high erythrocyte sedimentation rate, presence of rheumatoid factor or ACPA, and persistent inflammation. The systemic nature of RA results in extra-articular disease in an estimated 40% of patients. These patients may experience higher rates of vasculitis, rheumatoid nodules, keratoconjunctivitis sicca, pericarditis, pleural effusions, and pulmonary fibrosis than patients without RA[12].

Causes of Rheumatoid Arthritis

Many possible causative agents have been identified, yet the etiology of the disease is still unknown. Women are affected by RA predominately more often than men and a possible reason includes the effects of estrogen on the immune system via a T-suppressor cell pathway. It is believed that a genetic component to RA may exist. Supporting evidence includes an increased incidence in individuals carrying an epitope in the third hypervariable region of the HLA-DRB chains. Although there is still uncertainty in the etiology of RA, HLA genotyping may help predict relative risk, disease severity, and response to therapy. Serum rheumatoid factor, an immunoglobulin with anti-IgG Fc specificity, is another genetic component that can be found in patients with RA. Rheumatoid factor is highly characteristic of RA but is not specific, so clinicians do not rely solely on this finding for diagnosis[5]. Twin studies have also shown that there is a hereditary component involved with RA as monozygotic twins have a higher incidence of RA than dizygotic twins[13]. The relationship has held for first degree relatives: they have a 1.5 increased risk of developing RA than individuals in the general population[14]. Another significant correlation is the link between RA and other diseases believed to have autoimmune pathogenesis[15]. There is an overlap between alleles of RA, lupus erythematosus, inflammatory bowel disease, multiple sclerosis, and ankylosingspondylitis[16]. Environmental factors, such as smoking, have also been implicated in causation. Some studies have suggested that cigarette smoking enhances the development of RA[17]. Infection is yet another environmental factor and may offer further

explanation as to the possible etiology of RA. One of the prime suspects for a microbial trigger to RA is the Epstein Barr virus (EBV). Other agents that have been suggested in the development of RA include mycoplasma, Proteus mirabilis, parvovirus, and retrovirus1. Further studies may elucidate the exact role these microorganisms play in the etiology of RA.

Diagnosis

Laboratory tests to diagnose RA definitively do not exist, but genetic tests are available to test for susceptibility. These factors do not guarantee that patients will develop the disease, but the chances for the possibility of occurrence are much greater than in the general population. The majority of individuals who have RA are positive for both HLA-DR beta and rheumatoid factor. These genetic factors are major determinants for RA; however clinicians cannot rely solely on these factors for diagnosis. Synovial fluid in the inflamed joint can also be analyzed for leukocytosis of neutrophils or lymphocytes, low glucose and complement levels, and protein levels approaching those in plasma[18]. This test is nonspecific for RA, yet it may be used as a means to confirm the presence of inflammatory arthritis. Clinical features aid in the confirmatory diagnosis.

Medications for Rheumatoid Arthritis

RA is a progressive disease. When left untreated, inflammation can start to develop in other parts of the body, causing various potentially serious complications that can affect other organs, such as the heart, lungs, and nerves could cause significant long-term disability. In recent years, there have been significant advancements in medicines for treating rheumatoid arthritis, but there is still no cure. Medications known as disease-modifying anti-rheumatic drugs (DMARDs) are considered the gold standard for RA treatment. The disease-modifying ant rheumatic drugs (DMARDs), or slow-acting antirheumatic drugs, are so named because it is thought that they modify the progression of RA by favorably altering the natural history of the disease, or slowing the development of joint erosions or joint destruction, as measured on joint radiographs[19]. DMARDs are generally prescribed shortly after diagnosis. The type of DMARD a doctor prescribes depends on several factors, including disease severity and the balance between the medication's benefits and potential side effects[20].

Appropriate treatment early in the course of RA is essential to maintain joint function. The longer active disease persists, the less likely the patient is to respond to therapy[21]. Evidence has shown that early treatment can control synovitis and may slow, or even stop, the

radiographic progression of the disease[22]. Disease-modifying antirheumatic drugs are slow-acting drugs which may take weeks to months to produce any clinical response. Patients need to be informed about the delayed action of these drugs and the need to persevere with the treatment. Prolonged therapy with disease-modifying anti-rheumatic drugs (DMARDs) requires long-term monitoring for toxicity and safety profile. DMARDs are not used for immediate analgesic or anti-inflammatory effects but rather for their long term beneficial effects in controlling disease activity. DMARDs are classified into two major classes: synthetic and biologic. Each will be discussed here separately.

Synthetic/Nonbiological DMARDs

Synthetic or non-biological DMARDs are still the most commonly used agents for the treatment of RA and include a wide array of drug classes. The most recent edition of the American College of Rheumatology (ACR) recommendations includes five synthetic disease-modifying anti-rheumatic drugs[23].

Methotrexate (MTX)

MTX is a widely used first-linesyntheticDMARD that can be used alone or in combination for the treatment of RA. The chemotherapeutic agent methotrexate is the most widely used conventional, DMARD; it is considered an “anchor drug” because of its effectiveness and tolerability as well as its potential to enhance the effectiveness of biologic agents[8]. In clinical trials, methotrexate significantly decreases symptoms of RA and slows joint destruction on radiography. Methotrexate may require dose reduction in patients with liver disease and it must be used with caution in renal dysfunction, it takes 6–8 weeks for the onset of its benefit. MTX can be given orally, intramuscularly, or subcutaneously. The usual starting dose is 7.5–10 mg per week and the dose is titrated up to 20–25 mg per week on a fortnightly basis. The bioavailability of oral MTX decreases with higher doses therefore subcutaneous MTX is used in patients with inadequate response despite dose escalation. MTX primarily is cleared via the kidneys with most being unchanged in the urine. Therefore, any fall in glomerular filtration rate results in sustained serum levels of the drug that may induce bone marrow or other toxicities. MTX is a folic acid antagonist drug. By binding to dihydrofolate reductase, MTX interferes with DNA synthesis and cell replication. For the dose used in RA, its main effect is believed to be due to the inhibition of enzymes involved in purine synthesis leading to the accumulation of adenosine and thus inhibiting the T cell

activation. About 60% of patients may experience mild toxicity, but more than 70% continue treatment with it at the end of the first year making it superior to other non-biologic DMARDs. MTX should not be used in patients with pre-existing bone marrow aplasia or cytopenias, immunodeficiency, severe hepatic disorders, or active infectious disease. Concomitant alcohol intake or hepatotoxic drugs are also contraindicated, however in clinical practice alcohol within the recommended limits for cardiovascular benefits is allowed. MTX is contraindicated in pregnancy and the women of childbearing age due to the risk of teratogenicity.

Sulfasalazine (SSZ)

SSZ contains an anti-inflammatory and an antibacterial agent (5-aminosalicylic acid and sulfapyridine). 6–12 weeks are required for the onset of its action. Tablets should be administered in evenly divided doses, preferably after meals at the recommended dosage range of 30–50 mg/kg/day. In clinical practice, SSZ dose is started at 500 mg/day and is increased by 500 mg weekly to 2.0–3.0 g/day.SSZ operates by impairing folate absorption. Only 15% of the drug is absorbed as an unchanged drug from the small intestine. SSZ is cleaved in the colon by bacterial enzymes to release acetylsalicylic acid and sulfapyridine. SSZ is excreted primarily by urine (as unchanged drug, conjugates, and acetylated metabolites) and in small amounts by feces. The mechanism of action of sulfapyridine is unclear but may involve inhibition of the transcription factors which are increased in inflammation.

The combination therapy of MTX, SSZ, and HCQ results in a better clinical outcome than MTX alone, MTX plus SSZ or MTX plus HCQ in patients with a poor response to MTX or another unaccompanied DMARD.The efficacy of SSZ plus MTX is uncertain in comparison to either drug alone. A molecular rationale for the failure of a combination of SSZ and MTX to be more efficacious than either drug given alone was provided in a Dutch study which found SSZ to be a potent inhibitor of the principal cell membrane transporter for folates as well as MTX, along with inducing cellular folate depletion.SSZ is safe to be used during pregnancy.

Hydroxychloroquine (HCQ)

HCQ is primarily used in combination with other DMARDs. In patients with mildly active RA, particularly those without poor prognostic features or with findings limited to mild

inflammatory arthritis and a positive antinuclear antibody test (in whom a distinction cannot be made between early RA and early systemic lupus erythematosus), HCQ is usually used rather than SSZ or MTX as the initial DMARD. It has a slow action onset of 2–6 months. The drug is metabolized in the liver and metabolites include desethyl hydroxychloroquine and desethylchloroquine. HCQ is excreted by urine as metabolites and up to 60% as unchanged drug. HCQ functions by interfering with antigen presentation and the activation of the immune response by increasing pH within macrophage phagolysosomes. The usual starting dose in adults is 400 mg/day which can be decreased to 300 mg/day after 3 months. No specific laboratory monitoring is required. HCQ is considered to be safe for use during pregnancy.

Leflunomide (LEF)

LEF is the newest of the commonly used DMARDs given with the loading dose of 100 mg/day for three days followed by 10–20 mg/day. To minimize the initial side effects, it is not uncommon to reduce or not give the loading dose particularly in elderly or patients with other co-morbid illnesses. Leflunomide is a prodrug in which the active metabolite is responsible for its activity. Its metabolism is hepatic to an active metabolite M1 (also known as teriflunomide), which accounts for nearly all pharmacologic activity. Further metabolism proceeds to multiple inactive metabolites that undergo enterohepatic recirculation. Enterohepatic recycling appears to contribute to the long half-life of this agent, like activated charcoal and cholestyramine substantially reduce plasma half-life. The drug is excreted both in feces and urine. Leflunomide is an immune-modulatory agent that primarily inhibits replication of activated lymphocytes by blocking the de novo synthesis of pyrimidines and, therefore, DNA. It also has a weak anti-inflammatory action.

Biologic DMARDs

Several classes of biologic DMARDs are available for the treatment of RA. Biologic agents are targeted to altera specific step in the pathogenesis of the inflammatory response associated with RA. Specifically, these agents inhibit pro-inflammatory cytokines such as tumor necrotic factor (TNF) or interleukin (IL) molecules, among other mechanisms. These agents carry specific safety warnings. Tumor necrosis factor is a pleiotropic cytokine that plays a key role in the inflammatory process of RA. TheTNF inhibitors work by binding to TNF-α and blocking its activity on cell surface receptors. The U.S. Food and Drug

Administration (FDA) has given five TNF inhibitors label approval for the treatment of RA[24]. Each agent has shown efficacy in improving clinical response, reducing damage assessed on radiography, and improving quality of life while decreasing disability. Several TNF inhibitors are approved for use as monotherapy, although the combination with methotrexate improves response in both early and established RA[25].

Etanercept

Etanercept is a dimeric fusion protein that consists of an extracellular portion of the human p75 TNF receptor linked to an Fc fragment of human IgG. Etanercept is a self-administered by subcutaneous injection and can be used as either monotherapy or in combination with methotrexate. Etanercept efficacy has been demonstrated in patients whose disease previously failed to respond tomethotrexate[26]. Etanercept efficacy has also been demonstrated in the treatment of early RAin methotrexate-naive patients[27]. Etanercept can be given subcutaneously once weekly (50-mg injection) or twice weekly (two25-mg injections given 3–4 days apart).

Infliximab

Infliximab is a chimeric antibody that combines marine and human IgG. Infliximab is approved in combination with methotrexate to reduce signs and symptoms, stall the progression of joint damage, and improve physical functioning in patients with moderate to severe RA. To prevent the formation of antibodies to this foreign protein, methotrexate must be administered concomitantly with infliximab. Infliximab is administered by intravenous infusion by a health care professional. Infliximab efficacy has also been demonstrated in the treatment of early RA and methotrexate-naïve patients.

Adalimumab

Adalimumab is a fully human monoclonal antibody specific to TNF and is produced using recombinant DNA technology. Adalimumab is self-administered as a subcutaneous injection and is approved for use as monotherapy or in combination with methotrexate.

Golimumab

Golimumab is a fully human anti-TNF IgG monoclonal antibody produced using recombinant DNA technology. The agent binds to both soluble and transmembrane TNF,

which allows for both receptor binding and inhibition of cytokine activity [28]. Golimumab is also indicated for use in combination with methotrexate. Additionally, golimumab is efficacious in patients who have not responded to other anti-TNF agents like etanercept, adalimumab, and infliximab[29].

Certolizumab

Certolizumab is a pegylated Fab fragment of humanized anti-TNF monoclonal antibody and can be administered with or without methotrexate.

Biologic DMARDs Side Effects and Safety Measures

Side effects

Risk of Tuberculosis

Tuberculosis (TB) infections were documented in patients with RA even before the biologic DMARDs were on the market. An increased number of cases occurred after the release of anti-TNF agents[30]. Because TNF-α regulates host defense against mycobacterial infections, inhibition of this cytokine increases the risk of new-onset TB infection and reactivation of latent tuberculosis infection (LTBI). Tuberculosis infection has been documented with all of the anti-TNF agents particularly in infliximab and adalimumab, although some studies suggest the risk is lower with etanercept[31]. In contrast to the anti-TNF agents, no causal link has been established between anakinra, abatacept, rituximab, or tocilizumab and either new-onset TB infection or reactivation of LTBI, although experience with tocilizumab in patients with LTBI is limited. Risk factors for TB infection include intravenous drug use, prison or health care occupation, homelessness, and a history of travel or residence in an area with a high prevalence of the infection.

Risk of Infection (vaccine-preventable infections)

Patients with RA are more susceptible to vaccine-preventable infections. One study estimated the risk of infectious complications to be 2-fold higher in patients with RA than in the general population[32]. This increased susceptibility is not likely dependent on treatment with immune-modulating biologic therapies alone. Other factors that may contribute to an increased risk of infection in patients with RA include immune system dysfunction attributable to the disease itself, comorbidities, nonbiologic immunosuppressive RA

therapies, and RA disease activity. Biologic therapy plays a role in an increased risk of infection. Specifically, the anti-TNF drugs block important signaling processes in the immune response, leading to greater susceptibility to bacterial and fungal pathogens. Regardless of the cause, the morbidity and mortality in patients with RA make vaccination screening and administration important.

Risk of Opportunistic Infections (Bacterial and fungal)

In addition to the increased risk of vaccine-preventable infections, biologic agents pose an increased risk of opportunistic bacterial and fungal infections. A boxed warning about the risk of serious, sometimes fatal Legionella and Listeria infections were recently added to the label of each of the TNF inhibitors[33]. The FDA adverse effect reporting system contained 80 cases of Legionella pneumonia in patients receiving TNF inhibitors between 1999 and 2010[34]. Of the 80 cases, 65% were receiving their respective anti-TNF agent for RA for a median of 10.4 months. All TNF inhibitors except certolizumab were linked with the incidence of Legionnaire's disease. Data from the French registry RATIO report the annual incidence rate of nontuberculosis opportunistic infections including Legionella and Listeria to be 151.6 per 100,000 patient years[35]. The same study found that monoclonal anti-TNF antibodies (specifically infliximab and adalimumab) rather than soluble TNF receptor therapy (specifical etanercept) and steroid use greater than 10 mg per day are independently associated with increased risk of opportunistic infection. Opportunistic fungal infections, particularly histoplasmosis, have been identified in patients treated with adalimumab, etanercept, infliximab, and certolizumab pegol. In 2008, the FDA required a strengthened label warning for opportunistic fungal infections on these drugs. This was prompted by several cases of histoplasmosis that were not initially recognized by health care professionals, thereby delaying treatment. Twelve of 21 of these cases were fatal[36]. Unfortunately, histoplasmosis infections often present atypically in anti–TNF treated patients. Once acquired, this population is at greater risk of more severe or disseminated disease. Special care should be taken in assessing for and recognizing these infections in patients taking biologic agents.

Risk of Cardiovascular Disease

Inflammatory diseases such as RA increase cardiovascular risk. The increased risk of cardiovascular disease (CVD) morbidity is estimated to be 2-fold higher than that of the

generalpopulation[37]. In addition to a higher prevalence of traditional CVD risk factors in patients with RA, the disease itself seems to confer additional risk factors These disease-specific risk factors include immune dysregulation, plaque instability, elevated thrombotic markers (fibrinogen, D-dimer), systemic inflammation, and impaired coronary reserve.

Risk of Heart Failure

Heart failure exacerbation and increased risk of cancer are described in anti-TNF prescribing information. A 2001 report from the American College of Cardiology identified several large-scale clinical trials that were stopped early because etanercept treatment failed to demonstrate a benefit on heart failure or mortality[38]. Also, a study of 150 patients with New York Heart Association (NYHA) class III and IV heart failure found treatment with infliximab increased mortality and hospitalization from heart failure exacerbation after just 28 weeks of treatment[39]. In 2003, a study from the FDA MedWatch program reported 38 new cases of heart failure and nine cases of heart failure exacerbation in patients receiving anti-TNF therapy[40]. Thirty-eight of these cases were in patients with RA; of the incident heart failure cases, 50% occurred in patients with no identifiable risk factors. Ten of the 38 cases occurred in patients younger than 50 years. The guidelines recommend avoiding any anti-TNF biologic in patients with NYHA class III or IV heart failure or in those with an ejection fraction of 50% or less. Not all data regarding anti-TNF biologics and heart disease are unfavorable. A recent study of more than 20,000 U.S. veterans with RA found that the use of TNF inhibitors was not associated with increased risk of heart failure and was associated with a decreased risk of stroke[41]. This study is further supported by the second study of patients with RA that found the use of anti-TNF agents was not associated with a greater risk of hospitalization for heart failure than nonbiologic DMARDuse[42]. Lastly, a review and meta-analysis found that anti-TNF therapy is associated with a reduced risk of all cardiovascular events, myocardial infarction, and stroke[43]. The study did not look at the risks of anti-TNF agents in heart failure specifically. Because of conflicting evidence in this high-risk population, more research is needed to determine best practices for the use of anti-TNF biologics in heart failure.

Risk of Hepatitis

It is well established that immunosuppression increases viral replication, although much of the existing data come from patients receiving chemotherapy for malignancy or long-term

immune suppression after transplant rather than in the RA setting. Tumor necrosis factor inhibitors may induce or exacerbate multiple sclerosis and reactivate hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Both rituximab and the anti-TNF agents have been implicated in viral replication and reactivation of hepatitis infections, whereas extremely limited data exist in the setting of HBV or HCV with the other biologic agents[44]. Although the risk of viral replication exists, the current ACR guidelines do not recommend universal HBV or HCV testing at baseline for patients initiating biologic therapy. The guidelines do suggest that if risk factors for hepatitis are present, the evaluation may include hepatitis B surface antigen (HBsAg), antibody (anti-HBs), or core antibody (HBcAb) testing and/or HCV antibody testing; however, no formal recommendation for specific screening procedures are made. In contrast, the CDC recommends every patient starting immunosuppressive therapy be screened for HBV with the HBsAg, anti-HBs, and HBcAb tests[45].

Table No. 1: Risk of Opportunistic Infections

Agent	Dose	Comments
Methotrexate	7.5–15 mg orally weekly (up to 20–30 mg weekly); may divide the weekly dose into 2 doses given 12 hours apart 10–25 mg once weekly IM or SC Hepatic impairment: use with caution Renal dysfunction: use with caution; consider a dose reduction of 50% with CrCl< 50 ml/minute	Nonbiologic DMARD of choice Teratogenic– avoid in pregnancy Bioavailability decreases with oral doses exceeding 7.5 mg SC administration may improve bioavailability and avoid GI toxicity
Leflunomide	100 mg daily orally for 3days; then 20 mg daily. Not recommended with pre-existing liver disease	Clinical efficacy is considered equivalent to methotrexate. Alternative to methotrexate if the patient is unable to tolerate methotrexate Teratogenic–avoid in pregnancy
HydroxyChloroquine	200–300 mg twice daily orally Adjust dose for severe renal dysfunction	Antimalarial drug low toxicity profile but the moderate clinical effect
Sulfasalazine	500–1000 mg daily orally; titrate to 1000 mg twice daily	May be used as monotherapy or as part of combination therapy
Minocycline	100 mg twice daily orally Hepatic impairment: use caution Renal dysfunction: use with caution; max 200 mg daily when CrCl< 80 ml/minute	A moderate reduction in RA progression compared with other nonbiologic agents

MAINSYNTHETIC DMARDs FOR THE TREATMENT OF RHEUMATOID ARTHRITIS

Safety Measures

Screening for LTBI has been shown to reduce the risk of reactivation. The ACR guidelines recommend screening for LTBI with a thorough assessment of the patient's medical history and with either the tuberculin skin test or interferon-gamma release assay (IGRA). This screening should take place before the initiation of any biologic DMARD therapy regardless of a patient's risk factors for LTBI. The optimal test for TB screening is unclear. The tuberculin skin test may be limited by the potential for false-negative results in patients with RA receiving immunosuppressant therapy or with immune compromising co morbidities[46]. The IGRA has similar sensitivity but improved specificity over the tuberculin skin test in patients with a history of BacilleCalmette-Guerin vaccine or past infection with a non-TB mycobacterium. The IGRA is more costly than the tuberculin skin test and may have reduced sensitivity in patients without intact immune systems. The ACR endorses the use of the IGRA in patients with a history of BacilleCalmette-Guerin vaccination. The guidelines caution that a negative TB screen should not be interpreted as excluding the possibility of infection, especially when clinical suspicion exists because of concomitant risk factors. A second screening can be considered 1–3 weeks after the initial negative screen to confirm results. The 2012 ACR guidelines recommend a stepwise approach to TB screening. Any positive tuberculin skin test (induration of greater than 5 mm in the immune-compromised patient) or IGRA should be followed by chest radiography. If chest radiography is suggestive of active TB, a subsequent sputum examination is indicated to check for active TB infection. Anti-TB therapy should be started in any patient with RA having active TB, and prophylactic therapy should be initiated in a patient with LTBI. According to the ACR guidelines, biologic therapy can begin or resume after complete treatment of active TB and after 1 month of anti-TB prophylaxis in a patient with LTBI. The 2012 ACR guidelines recommend annual screening for patients receiving long-term biologic therapy who live, work, or travel where TB exposure is likely to occur.

To reduce the risk of infection, vaccines should be administered before anti- TNF agent initiation. The ACR guidelines recommend that before biologic therapy initiation, the inactivated influenza vaccine, recombinant pneumococcal vaccine, recombinant human papillomavirus vaccine, and live attenuated herpes zoster vaccine be administered to patients

deemed appropriate by the current Centre for Disease Control and Prevention (CDC) vaccination schedule. Additionally, the HBV vaccination should be considered before biologic therapy for any patient with risk factors for the disease. Live vaccines should not be administered during treatment. Risk factors for HBV include intravenous drug abuse, multiple sexual partners in the previous 6 months, and occupational setting such as health care or the prison system. The 2013 CDC schedule recommends annual influenza vaccinations in adults, a three-dose series of the human papillomavirus vaccine in men and women 19–26 years of age, herpes zoster vaccination once after age 60, and a three-dose series of HBV vaccination in at-risk individuals. The pneumococcal polysaccharide (PPSV23) vaccination should be given to adults (older than 19 years) with RA followed by a one-time revaccination 5 years after the first dose. The CDC also recommends that individuals at least 65 years of age receive one-time revaccination if they were vaccinated more than 5 years previously and the primary vaccination was given before age 65[47]. According to the ACR guidelines, live vaccines are contraindicated during biologic therapy; however, the guidelines do not address the minimum interval to wait after administration of a live vaccine before biologic therapy initiation. Guidelines from three countries (i.e., Great Britain, India, and Canada) recommend waiting 4 weeks between the administration of a live vaccine and initiation of biologic therapy[48]. Inactivated vaccines are generally considered acceptable for patients taking immunosuppressive drugs. The ACR guidelines recommend concomitant administration of biologic therapy with the inactivated influenza vaccine, pneumococcal vaccine, human papillomavirus vaccine, and HBV vaccine for appropriate patients.

Synthetic DMARDs Side Effects and Safety Measures

Side Effects

Methotrexate (MTX)

The most common side effects are nausea and vomiting for which folic acid has been reporte d to be beneficial[49] the day after the dose is taken. Mouth ulcers, reversible alopecia, rash, and increased rheumatoid nodule formation are also reported as a side effect. Rarer adverse effects include bone marrow suppression, liver cirrhosis (increased with alcohol consumption), and pulmonary infiltrates/allergic pneumonitis.

Most of the other side effects are mild & reversible Hepatic toxicity is one of the main

potential serious adverse reactions with MTX use, but the exact mechanism is not clearly understood[50]. Hematological abnormalities are rare with t he use of methotrexate. The main toxic effects described include macrocytic anemia, leucope nia, thrombocytopenia, and pancytopenia[51].MTX has been reported to have caused fetal death and congenital abnormalities and therefore its use is not recommended for use in pregnancy. It is suggested that pregnancy is avoided for a minimum of 3 months after c ompletion of therapy in male patients and at least one ovulatory cycle in female patients. Generally, many of the side effects of MTX are due to the inhibition of folate metabolism (e.g. nausea, stomatitis, bone marrow suppression). However, enthusiasm for the use of MTX is limited by two potentially serious adverse reactions which may not resolve with cessation of treatment:

Liver disease: Methotrexate-induced liver disease is characterized by fibrotic changes that may progress to cirrhosis. Initial studies estimated the incidence and seriousness of MTX induced liver disease. The incidence of renal toxicity is probably in the order of 1 in 1,000 RA patients over a 5-year treatment period. While the routine liver biopsy is not recommended, patients who have the persistent elevation of aspartate aminotransferase (AST) may require a liver biopsy to ensure that the continuation of treatment is not harmful.

Interstitial pneumonitis: This is an uncommon but potentially fatal complication of MTX treatment. The risk factors for MTX lung are not well understood but may include pre-existing lung disease or an abnormal chest radiograph. Patients taking MTX who present with a dry cough, shortness of breath on exertion, malaise, fever, and diffuse crackles on auscultation should discontinue taking MTX until evaluated further.

Sulfasalazine (SSZ):

Gastrointestinal intolerance is the most frequently reported side effect. Symptoms include anorexia, nausea, vomiting, loss of appetite, abdominal discomfort, and diarrhea [52]. Skin rash, hematological abnormalities, and pruritis are also side effects of SSZ. Neurological symptoms of headache, dizziness, or depression also occur. In males, oligospermia with impaired motility is also observed. This, however, does not act as a contraceptive and reverses three months after treatment is stopped. Rarer adverse effects include leucopenia, bone marrow depression, and hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency, abnormal liver function tests, hepatitis, and abdominal pain. As

SSZ inhibits the absorption of folate, it can cause folate deficiency. SSZ should not be prescribed for patients who are hypersensitive to salicylates or sulfonamide derivatives. It is also contraindicated in patients with hematological, renal, or hepatic dysfunction. Intolerance and adverse events are frequently associated with sulfasalazine administration.
More severe (and potentially fatal) hepatotoxicity has been reported in association with drug reaction with eosinophilia systematic symptoms and hypersensitivity reaction thought due to the sulfapyridine metabolite.

Hydroxychloroquine (HCQ):

Common side effects include epigastric burning, nausea, bloating, diarrhea, skin rashes, and alopecia. HCQ may also exacerbate psoriasis and patients may develop hyperpigmentation in sun-exposed areas. Retinal toxicity with macular damage is infrequent; however it is recommended that patients wear sunglasses in strong sunlight. Corneal risk increases if the dose exceeds 6 mg/kg/day and may result in blindness. Patients with pre-existing maculopathy should not take HCQ. Bone marrow suppression is rare, but potentially fatal agranulocytosis or aplastic anemia can occur. Central nervous system side effects are common and include headache, light-headedness, insomnia, nervousness, nightmares, and confusion.

Protocols and practices vary worldwide, however, it is generally recommended that ophthalm ological examinations are performed yearly. Local protocols should be established between the prescribing physician and the treating ophthalmologist.

Retinal abnormalities should prompt immediate cessation of the medication.

Leflunomide (LEF):

A range of potential adverse effects may occur in LEF. It has been reported in some patients to potentiate the action of warfarin as a result of its mutual competition at the level of cytochrome metabolism.

Hypertension: A small percentage of patients with RA develop hypertension when taking LEF. Concurrent therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) is a risk factor. Diarrhea may be more severe with a loading dose. Threefold elevation of serum aminotransferases (liver) has been noted in patients treated with LEF[52].

Hematology: Hematologic toxicity primarily results from an interaction between LEF and other drugs. LEF may enhance the bone marrow toxicity of MTX, possibly leading to pancytopenia, agranulocytosis, or thrombocytopenia.

Table No. 2: Synthetic DMARDs Side Effects and Safety Measures

Agent	Class	Dose	Frequency
Abatacept	T-cell co stimulation Modulator	IV:< 60 kg: 500 mg 60–100 kg: 750 mg > 100 kg: 1000 mg Sc 125 mg	Weeks 0, 2, 4, then monthly Weekly May be initiated with or without single IV loading dose If using loading dose, use weight-based dose above and start SC injection within 24 hours of the initial IV infusion
Adalimumab	TNF-α inhibitor	TNF-α inhibitor	Every 14 days. May increase dose to 40 mg every week in patients not taking methotrexate.
Anakinra	IL-1receptor antagonist	100 mg SC	Daily
Certolizumab	TNF-α inhibitor	400 mg SC, followed by 200 mg SC	400 mg SC weeks 0, 2, and 4, followed by 200 mg SC every 2 weeks
Etanercept	TNF-α inhibitor	50 mg SC; 25 mg SC	Weekly; twice weekly
Golimumab	TNF-α inhibitor	50 mg SC	Monthly Combine with methotrexate
Infliximab	TNF-α inhibitor	3 mg/kg IV infusion	Weeks 0, 2 and 6; then every 8 weeks Combine with methotrexate
Rituximab	Anti–CD 20	1000 mg IV plus	Days 1 and 15 may retreat every 24 weeks (no sooner than every 16 weeks) Combine with methotrexate
Tocilizumab	IL-6 receptor antagonist	IV: 4 mg/kg; may increase to 8 mg/kg SC: 162 mg	Every 4 weeks < 100 kg: every other week; increase to every week based on clinical response ≥ 100 kg: every week
Tofacitinib	Janus kinase enzyme inhibitor	5 mg PO	

BIOLOGIC DMARDs FOR TREATMENT OF RHEUMATOID ARTHRITIS

Safety Measure

Methotrexate is associated with several potentially serious adverse effects & therefore its use requires monitoring with blood tests and with close clinical supervision from a medical speci alist familiar with the potential risks.

Blood pressure monitoring is recommended during the first months of treatment or if NSAID therapy is begun at a later date. Patients with pre-existing liver disease should not receive LEF.Patients with elevated liver enzymes (alanine aminotransferase) greater than two times the upper limit of normal should not receive LEF. Caution should be used in patients who are taking other drugs that can cause liver injury. Liver enzymes should be monitored at least monthly for 3 months after starting LEF and at least quarterly thereafter. Leflunomide should not be given to patients with severe immunodeficiency, impaired bone marrow function, or severe uncontrolled infections. As liver impairment is also a complication, excessive alcohol consumption should be avoided. As Leflunomide inhibits Cytochrome P450 2C9, it can interfere with drugs such as phenytoin and warfarin.

It appears to be a particular risk when used in combination with methotrexate. Sulfasalazine t herapy also requires specialist supervision particularly concerning the frequent risk of adverse effects. Also, regular monitoring with blood tests is recommended.

CONCLUSION

Several adverse side effects associated with disease-modifying anti rheumatism drugs in rheumatoid arthritis patients. To address the severe side effects in the medication of RA patients, screening is mandatory before starting, resuming, or significantly increasing therapy with synthetic or biologic DMARDs which includes:

All patients should be screened for complete blood count (CBC), serum creatinine, and aminotransferases.

Before methotrexate (MTX), leflunomide (LEF) or biologic DMARDs—screening for hepatitis B and C should be performed in patients at increased risk.

All patients being considered for a biologic therapy must be screened to exclude the risk of any infection, including TB. If serious infections are evident before treatment, they should be reviewed by the prescribing physician and fully resolved before considering treatment with a biologic. When a serious infection develops, treatment should be stopped and only restarted once the infection has completely resolved. AR patients receiving TNF-α inhibitors should receive the pneumococcal vaccine, and inactivated influenza vaccine annually and also vaccinated against hepatitis B.

A chest radiograph is recommended in patients with a history of other risk factors for latent TB, and skin testing should be repeated in patients with new TB exposures.

Synthetic DMARDs use in the treatment of the rheumatic disease requires monitoring with a blood test and close clinical supervision to ensure that the potential side effects are minimized.

REFERENCES

1. McInnes IB, Schett G. Pathogenetic insights from the treatment of rheumatoid arthritis. The Lancet. 2017:389(10086):2328-37.
2. Furst DE, Breedveld FC, Kalden JR, et al Updated consensus statement on biological agents for the treatment of rheumatoid arthritis and other rheumatic diseases. Annals of the Rheumatic Diseases.2002:61(Suppl 2): ii2-ii7.
3. Cotran R, Kumar V, Collins T. Robbins Pathologic Basis of Disease. 6th Ed. Philadelphia, PA: W.B. Saunders Company:1999:1248-1251
4. Pavelka K, Kavanaugh AF, Rubbert-Roth A, Ferraccioli G. Optimizing outcomes in rheumatoid arthritis patients with inadequate responses to disease-modifying anti-rheumatic drugs. Rheumatology. 2012;51(Suppl 2): v12-v21
5. Wasserman A. Rheumatoid Arthritis: Common Questions About Diagnosis and Management. American family physician. 2018:1:97(7).
6. Hunter TM, Boytsov NN, Zhang X, Schroeder K, Michaud K, Araujo AB. Prevalence of rheumatoid arthritis in the United States adult population in healthcare claims databases: 2004–2014. Rheumatology international. 2017:1:37(9):1551-7.
7. Huizinga TW, Pincus T. In the clinic. Rheumatoid arthritis. Annals of internal medicine.2010:153(1):ITC1-1-ITC1-15: quiz ITC11-16.
8. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis and rheumatism.2010:62(9):2569-2581.
9. Van Nies JA, de Jong Z, van der Helm-van Mil AH, Knevel R, Le Cessie S, Huizinga TW. Improved treatment strategies reduce the increased mortality risk in early RA patients. Rheumatology (Oxford, England). 2010:49(11):2210-2216.
10. Spector TD: Rheumatoid Arthritis. Rheum Dis Clin North Am:1990:16:513-537
11. Catrina AI, Joshua V, Klareskog L, Malmström V. Mechanisms involved in triggering rheumatoid arthritis. Immunological reviews. 2016:269 (1):162-74.
12. Pieringer H, Pichler M. Cardiovascular morbidity and mortality in patients with rheumatoid arthritis: vascular alterations and possible clinical implications. QJM 2011:104:13-26.

13. Silman AJ, Macgregor AJ, Whiting S, et al: Twin concordance rates for rheumatoid arthritis: Results from a nationwide study. Br J Rheumatol; 1993:32:903-907.
14. Macgregorn AJ, Sieder H, Rigby AS, et al: Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. Arthritis Rheum; 2000: 43:30-37.
15. Mateen S, Moin S, Khan AQ, Zafar A, Fatima N. Increased reactive oxygen species formation and oxidative stress in rheumatoid arthritis. PloS one. 2016:11(4):1-15.
16. Jawaheer D, Seldin MF, Amos CI, et al: A genome-wide screen in multiplex rheumatoid arthritis families suggests genetic overlap with other autoimmune diseases. Am J Hum Genet.2001:68:927-936.
17. Padyukov L, Silva C, Stolt P, et al: A gene-environment interaction between smoking and shared epitope genes in HLA-DR provides a high risk of seropositive rheumatoid arthritis. Arthritis Rheum. 2004:50:3085-3092.
18. NIWA Y, LIO A, NIWA G, ET AL: Serum albumin metabolism in rheumatic diseases: relationship to corticosteroids and peptic ulcer. J Clin Lab Immunol. 1990: 31:11-16.
19. Lannuzi, L., Dawson, N., Zein, N. et al., Does drug therapy slow radiographic deterioration in rheumatoid arthritis? N Engi J Med 1983:309: 1023-1028.
20. Joseph B. All about rheumatoid arthritis.https://www.everydayhealth.com/rheumatoid-arthritics/guide/
21. Anderson JJ, Wells G, Verhoeven AC, Felson DT: Factors predicting response to treatment in rheumatoid arthritis: the importance of disease duration. Arthritis Rheum; 2000:43:22-29.
22. Lee DM,Weinblatt ME: Rheumatoid arthritis. Lancet; 2001:358:903-911.
23. Singh JA, Furst DE, Bharat A, et al. 2012 Update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res 2012:64(5):625-39.
24. Scott DL, Kingsley GH. Tumor necrosis factor inhibitors for rheumatoid arthritis. NEJM 2006:355:704-12.
25. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann of Internl Med1999:130:478-86.
26. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. NEJM 2000:343:1586-93.
27. Nam J, Emery P. Aspects of TNF inhibitor therapy in rheumatoid arthritis. Mod Rheumatol.2010:20:325-30.
28. Smolen JS, Kay J, Doyle MK, Landewé R, Matteson EL, Wollenhaupt J, Gaylis N, Murphy FT, Neal JS, Zhou Y, Visvanathan S. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor α inhibitors (GO-AFTER study): a multicentre, randomized, double-blind, placebo-controlled, phase III trial. The Lancet. 2009:18:374(9685):210-21.
29. Gardam MA, Keystone E, Menzies R, Manners S, Skamene E, Long R, et al. Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. Lancet Infect Dis 2003:3:148-55.
30. Tubach F, Salmon D, Ravaud P et al. Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: the three-year prospective French research axed on tolerance of biotherapies registry. Arthritis Rheum 2009:60:1884-94.
31. Gluck T, Muller-Ladner U. Vaccination in patients with chronic rheumatic or autoimmune diseases. Clin Infect Dis 2008:46:1459-65.
32. Smith JA, Kauffman CA. Endemic fungal infections in patients receiving tumor necrosis factor-alpha inhibitor therapy. Drugs 2009:69:1403-15.
33. FDA drug safety communication: drug labels for the tumor necrosis factor-alpha blockers now include warnings about infection with legionella and listeria bacteria. 2011:7.
34. Salmon-Ceron D, Tubach F, Lortholary O, et al. Drug-specific risk of nontuberculosis opportunistic infections in patients receiving anti-TNF therapy reported to the 3-year prospective French RATIO registry. Ann Rheum Dis 2011:70:616-23.
35. FDA: Manufacturers of TNF-blocker drugs must highlight the risk of fungal infections. FDA News Release.2008.
36. Avina-Zubieta JA, Thomas J, Sadatsafavi M, et al. Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis. 2012:71:1524-9.

37. Louis A, Cleland JG, Crabbe S, et al. Clinical trials update: CAPRICORN, COPERNICUS, MIRACLE, STAF, RITZ-2, RECOVER, and RENAISSANCE and cachexia and cholesterol in heart failure. Highlights of the scientific sessions of the American College of Cardiology, 2001. Eur J Heart Fail 2001:3:381-7.
38. Chung ES, Packer M, Lo KH, et al. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure(ATTACH) trial. Circulation 2003: 107:3133-40.
39. Kwon HJ, Cote TR, Cuffe MS, et al. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. Ann Intern Med 2003:138:807-11.
40. Al-Aly Z, Pan H, Zeringue A, et al. Tumor necrosis factor-alpha blockade, cardiovascular outcomes, and survival in rheumatoid arthritis. Transl Res 2011: 157:10-18.
41. Solomon DH, Rassen JA, Kuriya B, et al. Heart failure risk among patients with rheumatoid arthritis starting a TNF antagonist. Ann Rheum Dis 2012. Published online November 15. 2012:Doi: 10.1136/annrheumdis-2012-202136.
42. Barnabe C, Martin BJ, Ghali WA. Systematic review and meta-analysis: anti-tumor necrosis factor-alpha therapy and cardiovascular events in rheumatoid arthritis. Arthritis Care Res (Hoboken) 2011:63:522-9.
43. Koo YX, Tan DS, Tan IB, et al. Hepatitis B virus reactivation in a patient with resolved hepatitis B virus infection receiving rituximab for malignant B-cell lymphoma. Ann Intern Med 2009:150: 655-6.
44. Weinbaum CM, Williams I, Mast EE, Wang SA, Finelli L, Wasley A, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. MMWR Recomm Rap 2008:57:1-20
45. Smith R, Cattamanchi A, Steingart KR, Denkinger C, Dheda K, Winthrop KL, Pai M. Interferon-gamma release assays for diagnosis of latent tuberculosis infection: evidence in immune-mediated inflammatory disorders. Current opinion in rheu. 2011:23(4):377-84.
46. CDC. Advisory Committee on Immunization Practices (ACIP) recommended immunization schedule for adults aged 19 years and older- United States, 2013. MMWR 2013:62:9-19.
47. Misra R, Sharma BL, Gupta R, et al. Indian Rheumatology Association consensus statement on the management of adults with rheumatoid arthritis. Indian J Rheumatol. 2008:3 Suppl: S1-S16.
48. Ortiz, Z., et al., The efficacy of folic acid and folinic acid in reducing methotrexate gastrointestinal toxicity in rheumatoid arthritis. A metaanalysis of randomized controlled trials. J Rheumatol, 1998:25(1):36-43.
49. West SG. Methotrexate hepatotoxicity. Rheumatic Disease Clinics of North America. 1997:23(4):883-915.
50. Cassidy J.T., P., R. E., Laxer R.M., Lindsley C.B, Textbook of Pediatric Rheumatology. 5th ed. Elsevier Sa unders;2005.
51. Van Rossum, M.A., et al., Sulfasalazine in the treatment of juvenile chronic arthritis:
a randomized, double blind, placebo controlled, multicenter study. Dutch Juvenile Chronic Arthritis Study Grou p. Arthritis Rheum, 1998:41(5): 808- 816.
52. Silverman, E., et al., Leflunomide or methotrexate for juvenile rheumatoid arthritis. NEngl J Med, 2005:352 (16): 1655-1666.