(International Print/Online Journal)

SJIF IMPACT FACTOR: 4.617
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume2, Issue 2, Page No: 520-530
March-April 2019

Side Effects of DMARDs in Rheumatoid Arthritis Patients

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Type of Publication: Original Research Paper
Conflicts of Interest: Nil

ABSTRACT
Rheumatoid Arthritis is a treatable cause of disability. Disease Modifying Anti Rheumatic Drugs (DMARDs) have been used over the last 50 years to provide symptomatic relief, reduce disease activity, disability and to prevent radiological progression. Conventional DMARDs are used as monotherapy or in combination, and include Methotrexate, Hydroxychloroquine, Leflunamide, and Sulfasalazine. Biologic response modifiers, which are genetically engineered protein molecules, are newer agents available for the treatment of various inflammatory joint diseases. Biologic therapies approved for use in inflammatory joint diseases are TNF alpha Inhibitors (Etanercept, Infliximab, Adalimumab), T cell modulators (Abatacept) and B cell depletes (Rituximab). However, all current immune modulating therapies have potential side effects and the decision to use a particular agent for treatment should be based on a thorough discussion of the benefits and risks with the patients. TNF alpha antagonists are being used to treat moderate to severe disease in patients who have contraindications, fail to respond or develop side effects to conventional systemic therapies. Side effects associated with DMARs are include infusion and injection site reactions, infections particularly reactivation of TB, CHF, multiple sclerosis, Renal toxicity, hepatotoxicity, alopecia, stomach upset, autoantibody formation and drug induced lupus, erythematosus, liver function abnormalities, hematological and solid organ malignancies.

Keywords: **A**lopecia, **B**one marrow depression, **C**ongestive heart failure, **D**MARDs, **R**heumatoid arthritis, **T**umor necrosis factor.

INTRODUCTION

Rheumatoid arthritis is a chronic and usually progressive inflammatory disorder of unknown etiology characterized by polyarticular symmetric joint involvement and systemic manifestations. Extra articular involvement including rheumatoid nodules, vasculitis, eye inflammation, neurologic dysfunction, cardiopulmonary diseases, lymphadenopathy and splenomegaly are manifestations of the disease [1]. There is little direct evidence available to support this view, as most prospective studies of DMARDs toxicity are short term, and under taken in selected patients monitored under drug trial protocols, long term out comes in clinical practice are much poorer than clinical trial data would suggest, and hence late adverse drug reactions occur [2]. Long term data derived from unselected patients seen in every day clinical practice would provide the most useful information for planning DMARDs treatment regimens in the outpatient setting.

Etiology:

The cause of RA is unknown. Genetic, environmental, hormonal, immunologic and infectious factors may play significant roles. Socioeconomic, physiological and lifestyle factors (tobacco use [3]), may influence the disease development and outcome. Genetic factors account for 50 % of the risk for developing RA [4]. About 60 % of RA patients in the US carry a shared epitope of the Human Leukocyte Antigen DR4 cluster (HLADR4). Genes other than those of the major histocompatability complex (MHC) are also involved. Results from sequencing genes of families with RA suggest the presence of several resistance and susceptibility genes, including PTPN22 and TRAF5 [5] .Sex hormone may play a role in RA, as evidence by the disproportionate number of females with this disease; it has amelioration during pregnancy, its recurrence in the early post partum period and it's reduced incidence in women using oral contraceptives. Hyperprolactinemia may be a risk factor for RA [6]. For many decades, numerous infectious agents have been suggested as potential cause of RA, including mycoplasma organisms, Epstein-Barr virus, rubella virus and porphyromonas gingivalis [7].

Risk factors:

These include menopause, age, smoking, stress, obesity and other autoimmune diseases.

Epidemiology:

Rheumatoid arthritis affects about 1 % of the world's population with relatively low variation in incidence among countries. It can occur at any age, with increasing prevalence upto the seventh decade of the life. The disease is 3 times more common in women. In people ages 15-45 years women predominate by ratio of 6:1 sex ratio is approximately equal among patients in the first decade of life and in those older than age 60 years [8]. Epidemiologic data suggest that a genetic predisposition and exposure to unknown environmental factors may be necessary for expression of the disease. The major histocompatability complex molecules, located on T lymphocytes, appear to have an important role in most patient with RA. These molecules can be characterised using human lymphocytic antigen typing. A majority of the patients with RA have HLA-DR4, HLA-DR1 or in the major histocompatability region. Patients with HLA-DR4 antigen are 3.5 times more likely to develop RA than those patients who have other HLA-DR antigens. There is a regional variation in the prevalence of RA. The incidence appears to be highest in Pima Indians (5.3 %), Chippewa Indians (6.8 %), and the lowest in people from China and Japan (0.2 % - 0.3 %) suggesting the possibility that genetic factors contribute to RA. Women who actively take oral contraceptives have a lower incidence of RA (0.3/1000 women/ year) compared with women who never took oral contraceptives (0.65/1000 women/ year) [9].

Clinical manifestations: [10]

- Persistent systemic polyarthritis of hands and feet
- Progressive articular deterioration
- Extra articular involvement
- Difficulty performing activities of daily living
- Pain on motion
- Limitation of motion
- Stiffness, swelling and deformity of the joints
- Tenderness
- Rheumatoid nodules

Complications:

Extra articular involvement may include rheumatoid nodules, vasculitis, pleural effusion, pulmonary fibrosis, ocular manifestations, pericarditis, cardiac conduction abnormalities, bone marrow suppression, and lymphadenopathy [1].

Diagnosis:

Laboratory tests [5],

- Rheumatoid factor assay
- C – reactive protein (CRP) level
- Complete blood count (CBC)
- Erythrocyte sedimentation rate (ESR)
- Anti nuclear antibody (ANA) assay
- Anti-cyclic citrullinated peptide (anti-CCP) and anti-mutated citrullinated vimentin (anti-MCV) assay
- Other diagnostic tests:
- Joint fluid aspiration
- Joint radiograph

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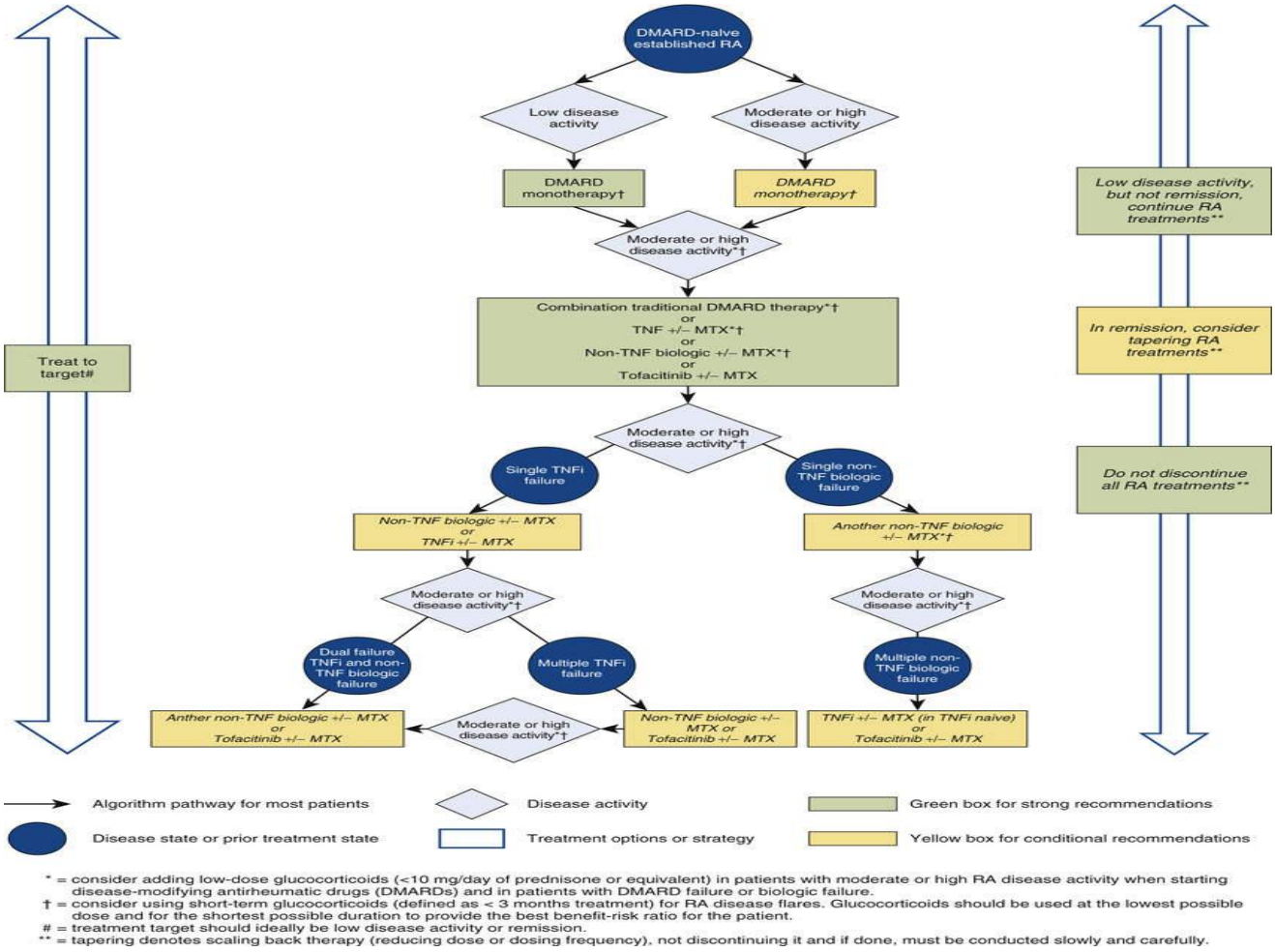
Figure 1: Algorithm for treatment of RA: [11]



* = consider adding low-dose glucocorticoids (<10 mg/day of prednisone or equivalent) in patients with moderate or high RA disease activity when starting disease-modifying antirheumatic drugs (DMARDs) and in patients with DMARD failure or biologic failure.
† = consider using short-term glucocorticoids (defined as < 3 months treatment) for RA disease flares. Glucocorticoids should be used at the lowest possible dose and for the shortest possible duration to provide the best benefit-risk ratio for the patient.
# = treatment target should ideally be low disease activity or remission.
** = tapering denotes scaling back therapy (reducing dose or dosing frequency), not discontinuing it and if done, must be conducted slowly and carefully.

Classification of DMARDs:

1. *Non-Biological DMARDs*
    a. Methotrexate
    b. Sulfasalazine
    c. Azathioprine
    d. D penicillamine
    e. Leflunomide
    f. Hydroxychloroquine
2. *Biological DMARDs*
    a. Etanercept
    b. Adalimumab
    c. Infliximab
    d. Abatacept
    e. Tocilizumab
    f. Rituximab

Side effects of non-biological DMARDs:

Methotrexate:

Dose: 7.5 – 15 mg orally/weekly (up to 20-30 mg weekly) [8].

Indication: Rheumatoid arthritis, Psoriasis, Connective tissue disorders (SLE, myositis, and Vasculitis), Crohn's disease, Felty's syndrome, Psoriatic arthritis [12].

Adverse effects: stomatitis, nausea, vomiting, thrombocytopenia, increased LFTs, chronic hepatotoxicity, photosensitivity, bone marrow suppression, pulmonary toxicity [13].

Methotrexate has multiple effects on various organs of the body. Mechanisms involved in the effects are as mentioned below:

a) Hepatic cellular damage:

MTX is demonstrated to increase the amount of hydrogen peroxide and stimulate neutrophils, leading to the release of other free radicals causing hepatic cellular damage [14], another mechanism include are deemed to be the result of oxidative stress due to reduction in glutathione content [15].

b) Thrombocytopenia:

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MTX induced activation of pro apoptotic proteins (Bid, Bax and Bad) through JNk (C-Jun-N-terminal kinase) phosphorylation leading to dissipation, cytochrome C release and caspase activation, culminating in apoptosis. MTX induces oxidative stress by altering the levels of ROS (reactive oxygen species) and glutathione cycle. Methotrexate promotes platelets apoptosis via Jnk mediated mitochondrial damage [16].

C) Stomatitis:

MTX is an inhibitor of dihydrofolate reductase, that reduces folate to an active form where it acts as a co factor for the production of nucleic acids essential for DNA synthesis. This effect on reducing DNA synthesis and cell turnover is responsible for both the therapeutic effect and the more common side effects. MTX mostly affects cells undergoing rapid turnover including mucosa and bone marrow, hence myelosuppression and stomatitis, mucositis is among the common reported adverse reactions [17].

Sulfasalazine:

Dose: 500 mg/day increasing by 500 mg weekly to 2-3 mg/day. Occasionally doses above 3 gm/day are prescribed. (Maximum dose is 40 mg/kg/day) [12].

Indication: Rheumatoid arthritis, Ulcerative colitis, Crohn's disease and sero negative Spondyloarthropathy including Psoriatic arthritis and Psoriasis.

Side effects: allergic skin reactions, nausea, vomiting, discoloration of the body fluids, reversible reduction in sperm count, bone marrow and liver toxicity, myelosuppression (thrombocytopenia, agranulocytosis, neutropenia, leucopenia or pancytopenia), increased liver enzymes, hair loss [18].

Sulfasalazine has multiple effects on various organs of the body. Mechanisms involved in the effects are as mentioned below:

a) Myelosuppression: (thrombocytopenia)

Drug induced thrombocytopenia is a rare cause of immune thrombocytopenia, with an estimated incidence of ten cases per million per year. The mechanism of sulfasalazine induced thrombocytopenia is drug dependent antibody induction which means drug induced antibodies that bind to platelet membrane proteins only in the presence of soluble drug in the serum. It leads to destruction of platelets [19].

b) Decreased sperm count:

Sulfasalazine has been reported to depress the fertility in men and experimental male animals, but the fundamental mechanism of infertility caused by sulfasalazine are still unknown. But the sperm motility and acrosome reactions; which are important for fertilization, were significantly reduced by sulfasalazine. Especially, CD59, which is located on the acrosomal membrane and is known to be important for the reproductive function of sperm, was affected by the sulfasalazine [20].

Azathioprine:

Dose: 1 mg/kg/day (initial), increasing after 4-6 weeks to 2-3 mg/kg/day. (maximum) [8].

Indication: Rheumatoid arthritis, Dermatomycetes, Polymyositis, Autoimmune and Chronic active Hepatitis, Pemphigus vulgarize [12].

Adverse effects: Principle and potentially serious toxic effects of Azathioprine are hematologic and gastrointestinal disturbances. Risk of secondary infections and malignancy are also significant. (Leucopenia, lymphoma, macrocytic anemia, myelosuppression, thrombocytopenia) [21].

Other adverse effects include fever, skin rashes, arthralgia, diarrhea, steatorrhea, negative nitrogen balance, reversible intestinal pneumonitis, and sweet's syndrome (acute febrile Neutrophilic dermatitis) [22].

Azathioprine has multiple effects on various organs of the body. Mechanisms involved in the effects are as mentioned below:

a) Macrocytic anemia :(Pure Red blood Cell Aplacia)

The mechanism involved in the development of PRCA is due to the excessive inhibition of DNA synthesis or direct cellular toxicity within the erythroid precursors brought about by the drug metabolite 6-thioguanine. Higher levels of this metabolite have been associated with bone marrow aplasia [23].

b) Sweet's syndrome:

Sweet's syndrome commonly known as acute febrile neutrophilic dermatosis, is a skin condition

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characterized by fever, inflammation of the joints, and painful skin lesions that appear mainly on the face, neck, back and arms. Azathioprine induced sweet's syndrome is rare and usually over looked. The mechanism involved in this is due to the azathioprine hypersensitivity syndrome, in this condition neutrophils or WBCs levels are increased it leads to the acute febrile neutrophilic dermatitis [24].

D-Penicillamine:

Dose: 125-250 mg/day; increased by 125 mg every 4 weeks up to 500 mg/day (if no response in 3 months consider an increase dose up to 750 mg/day) [25].

Indication: Rheumatoid arthritis and Wilson's disease.

Adverse effects: Bone marrow suppression, Dysgeusia, GI disturbances, proteinuria [26].

D-Penicillamine has multiple effects on various organs of the body. Mechanisms involved in the effects are as mentioned below:

A. Proteinuria:
   D penicillamine act through the diverse mechanisms producing injury, including direct damage to cellular and membranous glomerular components, as well as to renal vasculator, and development of nephrotic syndrome in patients. In several cases, the proliferation of mesangial cells and expansion of mesangial matrix were also noted. All these factors increase the glomerular injury. A common sign of glomerular injury is proteinuria [27].
B. Dysgeusia:
   Copper plays an important role in the physiology of taste by bimetallic stimuli Zn/Cu. D penicillamine decreases the copper levels in the body; it may lead to the disturbances in the copper mediated taste sensation ultimately leading to Dysgeusia [28].

Leflunomide:

Dose: 100 mg/day orally for 3 days, then 10-20 mg/day [8].

Indication: Rheumatoid arthritis and Psoriatic arthritis (not used in psoriasis) [12].

Adverse effects: GI disturbances, weight loss, alopecia, rashes, mouth ulcers, headache, diarrhea, raised liver enzymes, cytopenias, hypertension, rarely peripheral neuropathy and pneumonitis [21].

Leflunomide has multiple effects on various organs of the body. Mechanisms involved in the effects are as mentioned below:

A. Weight loss:
   One mechanism by which leflunomide may induce weight loss may be by interfering with oxidative phosphorylation and ATP generation in the mitochondria. Leflunomide induces the dihydroorotate dehydrogenase, a flavin linked enzyme that typically catalyses specialized oxidoreduction that is not in the mainstream of with transport. However, like other flavin linked enzymes, it may nonspecifically inhibit the mitochondrial transport chain by uncoupling oxidative phosphorylation. Further studies are necessary to determine whether leflunamide associated weight loss in the result of increased catabolism from inefficient ATP generation in the mitochondria [29].
B. Alopecia: Hair loss may be wide or localized spread. T lymphocytes and proinflamatory cytokines, like tumor necrosis factor alpha, would be responsible for hair growth inhibition due to its inflammatory action on hair bulb. Leflunamide hinders the interaction of T cells with antigen presenting ones and it leads to increases in the inflammatory infiltrate of T-lymphocytes around hair follicles, leading to hair loss [30].

Hydroxychloroquine:

Dose: 200-300 mg/orally/twice daily: Maximum dose-should not exceed 6.5 mg/kg body weight/day [25].

Indication: Rheumatoid arthritis, Connective tissue disorders (systemic and discoid lupus) [12].

Adverse effects: GI complaints, skin reactions, headache, retinal damage [8].

Mechanism of Hydroxychloroquine induced Retinal damage:

Hydroxychloroquine affects the metabolism of retinal cells and also binds to melanin in the retinal pigment

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epithelium (RPE). Melanin is the dominant light absorber in retinal pigment epithelium, which protects the cell from damage caused by oxidative stress. The loss of RPE melanin due to the hydroxychloroquine is risk factor for both retinal damage and a symptom of macular degeneration [31].

BIOLOGIC DMARDs

Side effects of biological DMARDs:

Etanercept:

Etanercept is a dimeric fusion protein that consists of an extracellular portion of human P75 TNF receptor linked to an Fc fragment of human Ig G [8].

Dose: 50 mg/SC/once weekly or 25 mg/twice weekly [25].

Indication: Rheumatoid arthritis, Psoriatic arthritis, Plaque psoriasis, and Ankylosing spondylitis [32].

Side effects: Risk of infections with Etanercept (opportunistic infections like mycobacterium tuberculosis, pneumocystis carini, candidiasis, cryptococcosis, aspergillosis and histoplasomosis were reported), autoimmunity and lupus like reactions, malignancy, lymphoma, demyelinating syndrome, congestive heart failure, headache, nausea, diarrhea, rashes, urticaria, pruritus, pyrexia, chest pain, angioedema, uveitis, scleritis, injection site reactions like erythema, itching, pain, swelling and hemorrhage [33].

Etanercept has multiple effects on various organs of the body. Mechanisms involved in the effects are as mentioned below:

A. Congestive heart failure: TNF alpha production could have an important role in heart failure, some studies suggested that normal levels of TNF act as cytoprotective responses in heart during acute ischemic injury, and below the normal levels are likely to play an important role in tissue remodeling and repair. TNF alpha induce contractile abnormalities by preventing a rise in intracellular calcium concentrations [35]. TNF alpha also stimulate nitric oxide production by stimulating iNOS. Etanercept acts as a carrier protein which stabilizes TNF results in the accumulation of high concentrations of immunoreactive TNF in the peripheral circulation, and TNF alpha form a complex with Etanercept then dissociate quite rapidly and it is speculated that the higher peripheral bioactivity may adversely affect the cardiomyocytes. In addition, Etanercept may also lead to enhanced TNF mediated effects by a second mechanism like alterations in the intracellular calcium levels and nitric oxide levels [34].

B. Demyelinating syndrome: TNFR 1, 2 receptors are essential for proliferation of immature oligodendrocytes, myelin repair and they also play important role in the onset of CNS autoimmune diseases. Etanercept induces CNS demyelination by reducing TNFR 1, 2 [35].

Adalimumab:

Adalimumab is a fully human monoclonal antibody specific to TNF and is produced using recombinant DNA technology [8].

Dose: 40 mg/SC/every 14 days may increase dose to 40 mg every week in patients not taking methotrexate [8].

Indication: Rheumatoid arthritis, Psoriatic arthritis, Ankylosing spondylitis, Crohn's disease, Plaque psoriasis [36].

Side effects: Mantle cell lymphoma, serious infections like Pneumonia, septic arthritis, prosthetic and surgical infections, erysipelas, cellulites, diverticulitis, urinary tract infections and reactivation of TB; nausea, abdominal pain, Injection site reactions (itching, hemorrhage, pain and swelling), headache, parathyroid disorders, lymphoma, low grade fever, weight gain, loss of or gain body fat and muscle [36].

Adalimumab has multiple effects on various organs of the body. Mechanisms involved in the effects are as mentioned below:

Reactivation of TB:

A. Tumor Necrosis Factor (TNF) plays a major pathogenic role in psoriasis and Rheumatoid arthritis but is essential for the host defense against mycobacterium and other granulomatous pathogens. Adalimumab

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decreases the levels of TNF to control the RA disease progression it is beneficial effect in RA patients but it may lead to increases the risk of reactivation of latent TB infection [37].

Weight gain:

B. Fat storage: It is understood that TNF can influence aspects of lipolysis and fat storage. Research suggests that high concentration of TNF alpha can induce fat loss or weight loss among the person with autoimmune conditions. Because Adalimumab blocks the action of TNF alpha individuals who have lost fat from high TNF alpha concentration may regain or store more body fat than usual. Any increase in fat storage throughout the body will account for some weight gain on Adalimumab [38].

Gut bacteria: Most evidence suggests that autoimmune disorders are associated with unfavorable changes in gut bacteria and that treatment with Adalimumab usually improves gut bacteria composition, that said, it is unclear as to whether all changes in gut bacteria during Adalimumab treatment are favorable, it's possible that Adalimumab might increase concentration of certain gut bacteria that stimulate appetite, cause bloating and /or increased fat storage – all of which are associated with weight gain [38].

Infliximab:

Infliximab is a chimeric antibody that combines murine and human Ig G. Infliximab is approved in combination with Methotrexate to reduce signs and symptoms in patients with moderate to severe Rheumatoid arthritis [8].

Dose: 3 mg/kg IV infusion, weeks 0, 2, and 6; then every 8 weeks to be combine with methotrexate Max dose: 10 mg/kg as often as every 4 weeks [8].

Indication: Rheumatoid arthritis, Crohn's disease, Ulcerative colitis, Ankylosing spondylitis, Psoriatic arthritis, Plaque psoriasis [39].

Side effects: sinusitis, cough, bronchitis, pruritus, abdominal pain, diarrhea, dyspepsia, fatigue, fever, headache, arthralgia, urinary tract infections, pneutropenia, peripheral demyelinating disorders, jaundice, hepatitis, cholestasis and malignancies like hepato splenic T cell lymphomas, lupus like syndromes, elevation of LFT's, activation of TB and hepatotoxicity (liver injury) [39].

Infliximab has multiple effects on various organs of the body. Mechanisms involved in the effects are as mentioned below:

A. Liver injury: The findings show that "liver injury associated with the use of TNF alpha antagonists is more common than previously reported, occurring in 1 in 120 of those exposed to Infliximab. Exactly how anti TNF agents cause liver injury remains unclear. Further studies show that Infliximab triggers CD4 T cells response associated with numerous human leukocyte antigen class 2 alleles react against liver cells. Infliximab causes disruption of liver homeostasis by blocking of sTNF alpha can promote the hepatocytes apoptosis and prevent or delay the process of liver regeneration [40].

Lupus:

B. The pathophysiology of the development of autoimmune disease in the setting of anti TNF alpha therapy is incompletely understood. In some cases of DIL associated with Infliximab, appears that neutralization of TNF alpha may stimulate humoral immunity to DNA and other nuclear antigens, leading to the production of auto antibodies [41]. Murine studies suggest that TNF blockade may induce humoral auto immunity by selectively inhibiting the induction of cytotoxic T lymphocytes that would typically suppress auto reactive B cell. Additionally, TNF alpha blockers may alter serum amyloid P or complement factors C1q or C4b all of which are mediated by TNF alpha and allow clearance of DNA through apoptotic antibodies. Without these factors' antinuclear autoimmunity and lupus like disease are observed [42].

Abatacept:

Abatacept is a selective T cell co stimulation modulator approved for the treatment of moderate to severe RA. It inhibits inflammation associated with RA by preventing the interaction between antigen presenting cells and T cells [8].

Dose:

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Route of administration	Body weight (kg)	Dose (mg)	Frequency
IV	<60	500	Weeks 0,2,4 then monthly
	60 – 100	750	
	>100	1000	
SC	---	125	Weekly once

Indication: Adults RA, Juvenile idiopathic arthritis, Psoriatic arthritis in adults [43].

Side effects: Frequently reported infections include – upper respiratory tract infections, bronchitis, herpes zoster, pneumonia, sinusitis, nasopharyngitis, urinary tract infections, development of malignancies, headache, dizziness, cough, back pain, dyspepsia, hypertension and swelling of the face (eyes, lips, throat, tongue) [43].

Abatacept has multiple effects on various organs of the body. Mechanisms involved in the effects are as mentioned below:

a) Pulmonary diseases:
The underlying mechanism has been suggested that the interference of CTLA-4 (Abatacept) signals in regulatory T cells result in the impaired suppressive functions of Th1, Th2 cells and in the exacerbation of T helper17(Th17) immunity. These T helper cells play an important role in maintaining mucosal barriers and contributing to pathogen clearance at mucosal surfaces, but they have also been implicated in autoimmune and inflammatory disorders. The loss of Th17 cell at mucosal surfaces due to presence of Abatacept has been linked to chronic inflammation and microbial translation results in pulmonary diseases [44].

b) Sinusitis, Nasopharyngitis and UTI:
In vitro and in vivo studies have demonstrated inhibition of immune response by Abatacept molecules, by down- regulation of T cell proliferation and inhibition of humoral immune response. Inhibition of the proliferation of both circulating naive and memory T cells has been observed during Abatacept therapy. Cell mediated immunity and humoral immunity plays a major defense role in the pathogenesis of infectious diseases, Due to the suppressed T cell and humoral immunity, infectious diseases like sinusitis, nasopharyngitis and UTI are more commonly seen in patients receiving Abatacept [45].

Tocilizumab:

It is a humanized monoclonal antibody that binds to interleukin 6 and inhibits its anti-inflammatory effect [8].

Dose: 4 mg/kg/IV every 4 weeks; Max-8 mg/kg/IV every 4 weeks. or 162 mg/SC/every week [46].

Indication: It is used to treat adult patients with moderately to severely active Rheumatoid arthritis [46].

Adverse reactions: Upper respiratory tract infections, nasopharyngitis, headache, hypertension, increased liver enzymes, dizziness, bronchitis, abdominal pain, rashes, gastritis, increased cholesterol, decreased neutrophil and platelet count [46].

Tocilizumab has multiple effects on various organs of the body. Mechanisms involved in the effects are as mentioned below:

a) Liver injury:
Kupffer cells secrete IL-6 which helps in the process of liver regeneration. Tocilizumab inhibits this pathway there by causing fatty infiltration in the liver which promotes apoptosis [47].

b) Neutropenia:
The mechanism of the Neutropenia with Tocilizumab (TCZ) is unknown, but IL-6 increases circulating neutrophil by releasing them from margination pools in bone marrow, thus TCZ may potentially reverse this effect by inhibiting the IL-6 release; it leads to

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decreased neutrophil count in the circulating blood. Another mechanism includes IL-6 increase the neutrophil count by increasing the IL-8 and Granulocyte macrophage colony stimulating factor levels mediated through decrease CD162 neutrophil expression. But TCZ decreases IL-8 and Granulocyte macrophage colony stimulating factor levels and could reverse the IL-6 mediated inhibition of CD162 neutrophil expression there by decreases the circulating neutrophil count [48].

Rituximab:

It is a genetically engineered chimeric monoclonal antibody that treats RA by depleting peripheral B cells [12].

Dose: TWO 1000 mg/IV infusions separated by 2 weeks [49].

Indication: Non-Hodgkin's lymphoma, Chronic Lymphatic Leukemia, Rheumatoid arthritis, Granulomatosis with polyangiitis, moderate to severe Pemphigus vulgarize [49].

Adverse reactions: Ventricular fibrillation, myocardial infarction, cardiogenic shock, Fever, flushing, urticaria, chills, pruritus, hepatitis B reactivation, renal toxicity, bronchospasm, nasopharyngitis and sinusitis [49].

Rituximab has multiple effects on various organs of the body. Mechanisms involved in the effects are as mentioned below:

a) Cardiovascular diseases:
The pathophysiology of Rituximab induced non ischemic cardiomyopathy remains unclear, the finding from Kanamori *et al* raised an important observation. After Rituximab infusion, patient's cardiac myocytes were noted to have diffuse amounts of reticulin fiber along with increased serum transforming growth factor beta levels. The investigators suggest that the transforming growth /growth factor beta levels could have led to increase reticular fiber formation causing a decrease in myocardial contractility leading to non-ischemic cardiomyopathy [50].
b) Lung diseases: The possible pathogenic mechanisms include the role of complement activation, cytokines, cytotoxic T lymphocytes and CD20 positive T cells. Rituximab increases the Cytotoxic T lymphocyte activation and produce vascular and alveolar damage. Disturbed cellular cytotoxicity, can also result from the interaction of Rituximab with CD20 and T cell or by cross reactivity between lungs tissue and humoral antigens with possible generation of a self-reactive clone. These self-reactive clones act against the lung tissues and causes alveolar damage, complement activation and cytokine secretion which could be the causative factors in side effects associated with Rituximab induced lung disease [51].

Conclusion:

The advent of anti TNF alpha and DMARDs therapy, both are important in the management of RA. However, reports about the safety of anti TNF alpha therapy, including a risk of serious infections, CHF, malignancy and multiple sclerosis have been accumulating in the literature. Additionally, the ACR guidelines provide algorithms to aid the clinician in the decision. Pharmacist can play an important role in patient education and drug selection for the patients with progressive Rheumatoid arthritis. Vaccination should be initiated before starting biological DMARDs therapy to avoid risk of infections.

Abbreviations:

DMARDs – Disease Modifying Anti Rheumatic Drugs

TNFR – Tumor Necrosis Factor Receptor

DIL – Drug Induced Lupus

TCZ – Tocilizumab

MTX - Methotrexate

CTLA4 – Cytotoxic T-Lymphocyte Associated protein 4

PRCA – Pure Red blood Cell Aplasia

TNF – Tumor Necrosis Factor

INOS – Inducible Nitric Oxide Synthase

LFT – Liver Function test

HLA – Human Leukocyte Antigen

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