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Therapeutic Drug Monitoring of Biologicals and Its Clinical Impact on Rheumatoid Arthritis: A Review

Tazneem B*, Neha Sultana; Nishath Begum; Bushra Noorie and Mohammed Tauqeed

Deccan School of Pharmacy, Darussalam, Hyderabad, India

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Abstract

Rheumatoid arthritis (RA) is a long-term inflammatory condition that mostly impacts joints, resulting in the progressive destruction of cartilage and bone and usually resulting in permanent disability. There are several pro-inflammatory cytokines that are involved in illness's development; these include interleukins (IL-1, IL-6 and IL-17), tumour necrosis factor-alpha (TNF-a), and macrophage-released mediators. These cytokines promote osteoclasts, which leads to bone erosion. Early RA diagnosis is important to enhance treatment response particularly in patients who are highly prognostically unfavourable including elevated disease activity, the existence of autoantibodies, and damage of joints. The RA management relies on frequent evaluations of disease activity using validated composite scores and using treat-to-target approach. Available treatment options comprise traditional synthetic, biological and recently developed disease-modifying antirheumatic medications that are not biological (DMARDs). Main objective is to reach at least minimal disease activity or remission, and only then it can be thought about gradual reduction of dose. The past few years have seen the development of biologic therapy drugs that are designed to enhance the management of RA by attacking major immune pathways including TNF-a (infliximab,IL-6, CD20 (rituximab), IL-1 (anakinra), etanercept, adalimumab, golimumab, certolizumab, and cytotoxic T lymphocyte-associated antigen-4(CTLA-4; abatacept).These agents have an action of suppressing inflammatory cytokines and regulation of immune reactions. Although biologics have significant clinical advantages, they are connected to both short and long-term negative events and can be used alone or with other antirheumatic treatment.

Keywords: Degenerative joint disorder, Rheumatoid arthritis, Inflammatory mediators, Therapeutic management of autoimmune diseases, Interleukins, TNF-α inhibitors, Biologic treatments.

Introduction

Rheumatoid arthritis (RA) is a long-term, systemic inflammatory autoimmune disease that mainly affects more than one joint resulting to pain, stiffness in morning, swelling and peripheral joint symmetries. During the onset, it might not manifest itself but as the disease advances, the destruction of the joints can be devastating.

***Corresponding Author:**
Tazneem B
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Later stages of RA frequently result in extra-articular complications like serositis, vasculitis, Felty syndrome, peripheral neuropathy, or pulmonary issues.

RA was first defined as a phenomenon (in 1800) by Landre-Beauvais and given a proper name in 1890 by Archibald Garrod. The disease is afflicted to about 1 percent of the total world population with the prevalence expected to increase to about 31.7 million people in the year 2050. Women represent an almost 69-percent prevalence. The traditional medications, including nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, have been proved to alleviate stiffness and pain but they do not slow down the development of the illness. The use of (DMARDS) or disease-modifying antirheumatic medications has been present in RA management since long. Introduction of biologic agents like etanercept, infliximab, and rituximab have really come as a blessing to clinical outcome but is constrained by high price, large molecular weight, poor tissue penetration and short half-lives. The restrictions have motivated the design of safer and more optimal therapeutic approaches that have better pharmacodynamics and pharmacokinetics. New biologics that inhibit TNF-alpha, Janus protein (JAK) and anti-interleukin-based antibodies aim at improving the efficacy and decreasing adverse effects. Abatacept (anti-CD80/86) Rituximab (anti-CD20) are the important agents used in the approach of treat-to target therapy.

Epidemiology

RA, is a common chronic inflammatory disorder that is experienced by about 0.5–1.0 %of people who are adults in the entire world. Its overall prevalence has not altered much; however, some significant higher rates have been seen in groups. Specifically, the burden of disease is higher in the Indigenous people of North America, with prevalence rates of 5.3 % in the case of Indian Pima community and 6.8 % in the case of Indian Chippewa population. It is estimated that close to 18.5 million individuals in the world are living with RA now (Global Burden of Disease study). Moreover, newly diagnosed cases are projected to increase at a substantial rate every year with an estimated average of close to 40 % of the 1.07 million cases in 2019 with some estimates showing that this figure is bound to go up to about 1.5 million by 2040. Rates of RA prevalence have been reported in epidemiological studies in India as 0.28 to 0.70 %.

Prevalence of Rheumatoid Arthritis Globally

RA was estimated to occur in approximately 7.9 million older adults across the world in 2021, with an estimated number of 5.69 and 2.23 million cases in women and men respectively. Its incidence in the entire world was reported to be 726.9 per 100,000 inhabitants. There was also a noticeable sex difference as women had a significantly higher prevalence rate (969.9 per 100,000) than that of men (445.7 per 100,000). In general, the probability of older women to develop RA was more than twice as high as it was among older men. This female domination was noted in every age range with the frequency of 257.3 cases per 100,000 in women and 227.1 cases per 100,000 in men.

Pathogenesis of Rheumatoid Arthritis

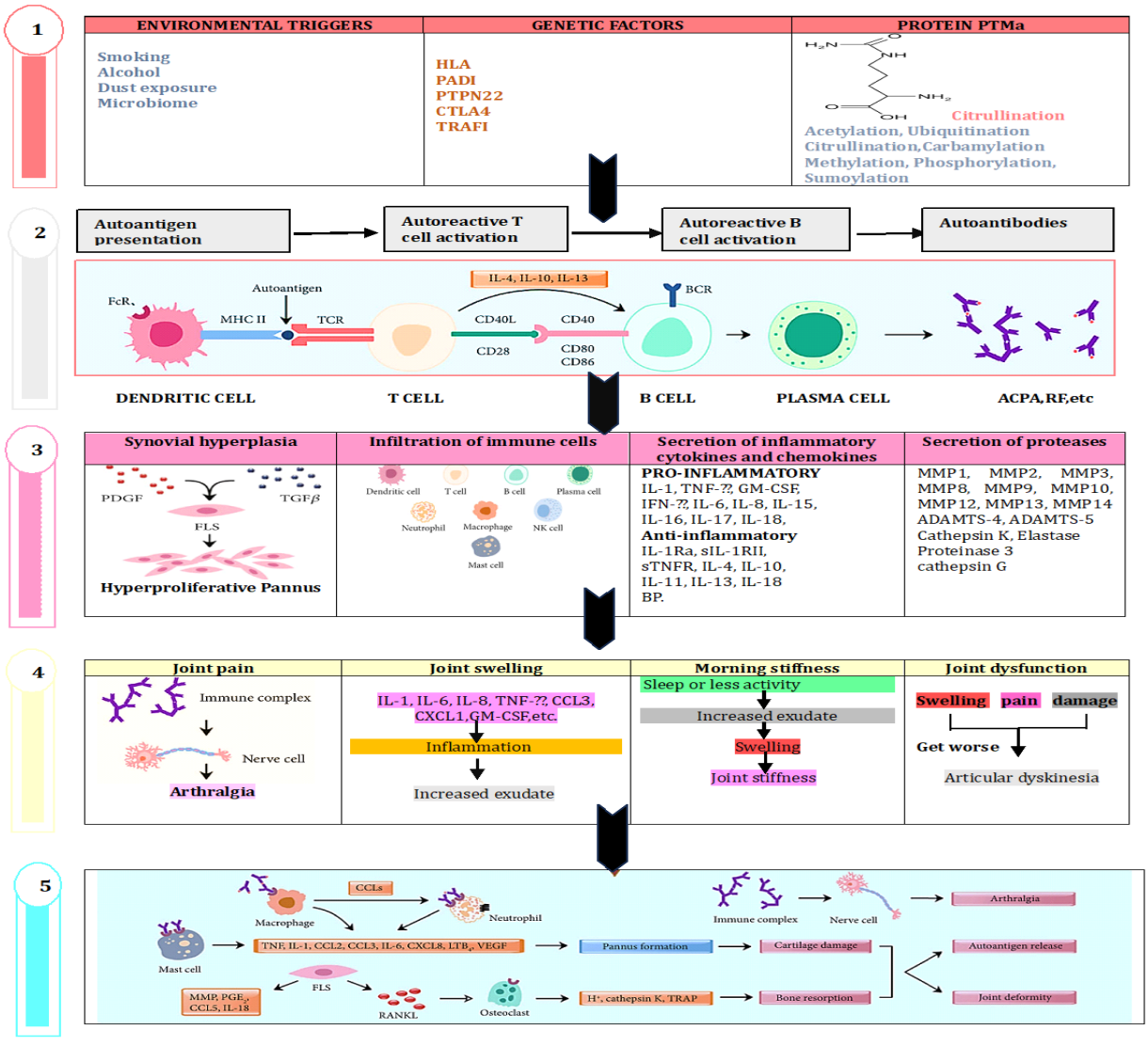
The symptoms of rheumatoid arthritis (RA) include excessive thickening within the synovial tissue, and this eventually results in the destruction of the affected joints. The pathogenesis and pathophysiology of RA are dependent on the complex interaction of environmental, genetic and epigenetic and factors. RA has been associated with more than 100 genetic susceptibility regions including the HLA class II alleles and non-HLA genes, some of which are PTPN22, PADI4, TRAF1, and CTLA-4, which raise the danger of developing the disease. The susceptibility to RA is further increased by environmental and lifestyle conditions, such as cigarette smoking, hormonal effects, periodontal infections, and a change in the gut microbiota. The development of the disease is accompanied by macrophages, immune cells, mast cells, neutrophils, dendritic cells, B lymphocytes, and T lymphocytes, in addition to non-immune cells, such as fibroblasts and chondrocytes. These cells actively participate in disease processes by the production of inflammatory mediators. Disease progression is associated with the release of a large range of harmful substances, such as autoantibodies, cytokines, chemokines, and proteolytic enzymes. A combination of these mediators results in

chronic inflammation, degeneration of cartilages, erosion of bones and progressive deterioration of the joints. Consequently, synovial membrane is the focus of inflammatory activity and a key therapeutic target in rheumatoid arthritis**.**

Inflammatory Processes and Disease Progression

Since the exact cause of RA is unknown, the, the pathology is linked with immune tolerance impairment to self-antigens, concomitant with the long-term activation of T and B lymphocytes. This immune imbalance leads to the invasion of inflammatory cells and autoantibodies into the joints, which causes the hyperplasia of the synovium and the increase in the size of destructive macrophages and fibroblasts. They lead to acceleration of the cartilage degeneration and erosion of bones and finally result in joint deformation and physical impairment. Extra-articular complications such as cardiopulmonary manifestations may also be involved with RA, indicating the systemic characteristics of the disease.

Inflammation is a rather pivotal factor during RA and can be evaluated with the help of such biomarkers like erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), in addition to using imaging and synovial fluid analysis. Proinflammatory cytokines, especially Tumour necrosis factor-alpha (TNF-A) and interleukin-6 (IL-6) are significantly increased in both blood and synovial fluid of RA patients and there are also anti-inflammatory cytokines like interleukin-10, which help to regulate the immune system. The liver produces the acute-phase protein known as CRP in reaction to the action of inflammatory cytokines and is a very effective marker of systemic inflammation and disease activity in RA.



Different phases in RA pathogenesis

Etiology

I) Genetic Factors

Pathogenic Role of HLA Genes

Autoimmune disease like Rheumatoid arthritis which is multi-factorial and develops as a result of epigenetic regulation, genetic predisposition, and environmental factors. The most important genetic factors are the major histocompatibility complex area, especially the HLA-DRB1 genes, which explain almost a third of inherited risk. HLA-DRB1 alleles have been demonstrated to have population-specific association and have a common amino acid sequence known as the shared epitope, which improves antigen presentation and facilitates T-cell-mediated autoimmune reactions. These are the strongest genetic risk factors of rheumatoid arthritis which are single epitope positive alleles. Even though the proportion of the susceptibility is explained by the HLA-DRB1, a number of non-HLA genes also play a role in the risk of the disease. Recent findings indicate that there are some HLA alleles that possibly provide a protective effect to certain groups of patients. Shared epitope positive HLA-DRB1 alleles have been regarded as the best genetic risk factors of RA. Genetic association and genetic association Genetic linkage and association studies have supported that HLA-DRB1 alone can be the explanation of about 30-40 percent of the inherited risk whereas the total genetic factors can be a contributor of about 60 percent of the disease predisposition. Besides HLA genes, non-HLA genes have been linked to the risk of RA as well, such as TRAF1/C5, PTPN22, IL2RB, AFF3, CTLA4, STAT4, CD6, CD40, KIF5A-PIP4K2C, CCL21, PADI4, TNFAIP3 and MMEL1. Interestingly, it is indicated by recent cohort studies that HLA-DRB1*1301 allele might play a protective role in ACPA-positive and ACPA-negative RA.

II) Environmental Factors

Exposure to Infectious Agents

Several infectious agents have been linked to the progression of RA. Chikungunya virus infection has been associated with persistent inflammatory arthritis that closely resembles RA in its clinical presentation. Evidence from both clinical observations and animal studies suggests that alterations in the microbiome may also play a role in RA pathogenesis**.** In particular, microorganisms such as Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Proteus mirabilis, and Mycoplasma species have been linked to disease initiation and progression. Among these, P. gingivalis is considered especially significant, as periodontal disease caused by this bacterium has been linked to a higher chance of developing RA.

III) Exposures Other Than Smoking

Air Pollution

A number of infectious agents have been contributing to the development of rheumatoid arthritis (RA). Chikungunya virus infection it has been linked with chronic inflammatory arthritis. Arthritis share many clinical similarities. Clinical findings and animal research evidence indicate that the microbiome modifications can also contribute to the RA pathogenesis. Specifically, the microorganisms that have been linked to the onset and advancement of the disease include Mycoplasma, Proteus mirabilis, Porphyromonas gingivalis, and Aggregatibacter actinomycetemcomitans types. Among them, P. gingivalis is regarded to be of special importance, because periodontal disease induced by this bacterium has been connected to an heightened chance of getting RA.

Silica Exposure

A major issue in the public health of people is the environmental air pollution that is mostly caused by the energy production and the industries. Development of autoimmune diseases has been attributed to major pollutants like ozone (O_3), carbon monoxide, sulfur dioxide (SO_2), nitrogen dioxide (NO_2), particulate matter (PM), and lead among others. Immune activation in the lungs is deemed a critical location in which inhaled pollutants can lead to airway injury, oxidative stress, epigenetic alterations, and systemic inflammation and thus are likely to result in the progression of RA.

IV) Lifestyle Factors

Tobacco-Smoking

The most significant environmental risk factor for rheumatoid arthritis development is known to be cigarette smoking. It is especially linked with a higher risk of ACPA-positive RA, although its role in ACPA-negative illness has also been mentioned. As a significant percentage of patients who have ACPA-positive RA are rheumatoid factor-positive, smoking is regarded as one of the major factors contributing to the illness progression.

Cigarette Smoke

The chronic smoking of cigarettes is one of the major contributors of various chronic diseases, including RA, due to changes in innate and adaptive immunity. They can cause changes in immunity that facilitate autoimmunity and predisposition to inflammatory joint disease. Case-control studies which were determined by the population the population revealed that participants who had smoked over a period of 20 years were almost three times more chance of getting RA that is ACPA-positive. and nearly 60% more ACPA-negative RA risk compared to non-smokers.

Alcohol

In the past, rheumatoid arthritis (RA) has been found to be decreased in the case of alcohol consumption. Population-based studies such as that carried out in Denmark have indicated that those who drink alcohol are less likely to develop ACPA-positive RA than none drinkers. It is found to have a dose-dependent protection effect with low to moderate levels of alcohol consumption demonstrating positive outcomes in regulating the immune system. Alcohol can also affect immune response, by changing the immune cell functions and gut microbiota, which results in more production of anti-inflammatory short-chain and polyunsaturated fatty acids, which in turn restrict inflammation.

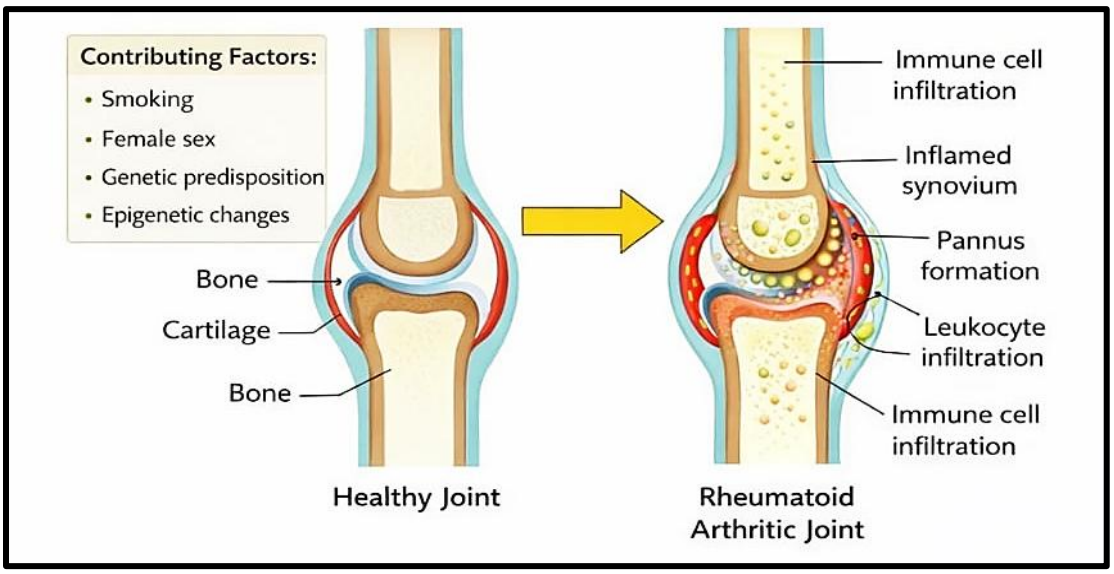
Vitamin D

Vitamin D is an important hormone required to keep the bones healthy and balanced with minerals as well as having a significant role in immune control. It interacts with the vitamin D receptor (VDR) to regulate both innate and adaptive immune responses mostly by inhibiting overactivity of inflammation. In addition to its participation in calcium phosphate homeostasis and bone mineralization, vitamin D has been shown to modulate immune balance in keeping pro-inflammatory Th1 and Th17 lymphocytes down and increasing regulatory T cells that restrain excessive immune responses. This has linked a high susceptibility to auto immune diseases like RA with vitamin D deficiency.

Pathophysiology of Rheumatoid Arthritis

RA synovial membrane synovitis (chronic inflammation of the synovial membrane) causes the synovial lining to thicken and the ultimate breakdown of bone and cartilage. In the normal circumstances, the synovium has one to two layers of the synoviocytes. In the event of inflammation, the presence of different types of immune cells like T lymphocytes, B lymphocytes, plasma, mast and dendritic cells, as well as macrophages are found in the synovial tissue. Such invasion of immune cells leads to synovial hyperplasia, which causes an increase in the synovial membrane and villous projections.

Macrophage-like synoviocytes generate high levels of pro-inflammatory cytokines, including tumor necrosis factor (TNF), interleukin-1 (IL-1), interleukin-6 (IL-6), that result in the sustained inflammation and joint destruction. Also, fibroblast-like synoviocyte (FLSs) release inflammatory mediators, such as IL-6, leukotrienes, and prostaglandins. These cells too have migratory features, becoming able to occur between joints and cause the progression of the disease.



Compares a normal joint with the structural modifications observed in RA

RA is a product of environmental and genetic influences. Smoking is a significant provocation, especially in patients positive in HLA-DRB1 common epitope is linked to the generation of anti-citrullinated protein antibody (ACPA)-positive. Seropositive RA is a characteristics of rheumatoid factor (RF) and autoantibodies. ACPA are the most significant markers. ACPA binds to citrullinated strains of APA target proteins whose surface has been altered by peptidyl arginine deiminase (PAD) enzymes. Target proteins are commonly vimentin, fibrinogen, fibronectin, histones and type II collagen. ACPA can be detected by cyclic citrullinated peptide (CCP) assays with high specificity to RA, and can use IgG, IgM, or IgA isotypes. There are other modified proteins which are also connected to RA's pathogenesis. The presence of anti-carP (anti-Carbamylated Protein) antibodies is detected as a result of homocitrulline that is created in the carbamylation reaction and can be found in ACPA-negative as well as ACPA-positive patients. Anti-acetylated protein antibodies are also reported indicating a relationship between activity, mucosal inflammation, and auto-immunity by microbes. The mucosal locations in most cases initiate the autoimmune process including the mouth,lungs, and digestive system. Smoking elevates the activity of PAD in the lungs, which causes the development of the citrullinated neoantigens. Porphyromonas gingivalis also contributes to periodontal inflammation that facilitates the alteration of proteins. These processes cause the synthesis of anti-modified protein antibodies (AMPAs) in genetically predisposed persons. The presence of autoantibodies may take several years before clinical arthritis develops which is a pre-clinical stage of RA. Development of symptomatic disease takes place when response of the immune system changes to the synovium. The features of established RA include the inflammation of the synovium with immune cells and the stimulation of the fibroblast-like synoviocytes leading to the release of pro-inflammatory cytokines: TNF, IL-6, and GM-CSF. These mediators influence chronic inflammation, cartilage, bone erosion, and systemic complications, such as cardiovascular disease.

Targeted Immunomodulation of Inflammatory Pathways

Biological agents have nowadays become widely applied in the management of rheumatoid arthritis since they interact with particular immune pathways that cause inflammation. They are very useful in the treatment of the diseases to slow the activities, prevent the damages of the joints and also in the improvement of the quality of life. Their action is better therapeutic with fewer side effects. In contrast to the side effects that are systemic and hence are a significant component of contemporary rheumatoid arthritis management. Rheumatoid arthritis treatment with biological agents could be categorized as follows:

I) TNF-A (tumor necrosis factor A) Inhibition

Adalimumab

Adalimumab is a fully human recombinant monoclonal antibody with tumor-like properties. (TNF- α) is necrosis factor-α. Antagonist belonging to the IgG1 subtype that selectively inhibits the primary pro-inflammatory cytokine, tumor necrosis factor-alpha (TNF-α), driving diseases caused by the immune system, like RA and inflammatory bowel disease (IBD). It binds with high affinity to both soluble and membrane-bound TNF-α, thereby preventing TNF-α from interacting with its cell surface receptors TNFR1 (p55) and TNFR2 (p75) on target cells. This antagonist action effectively reduces synivial inflammation , disease activity, ans progressive joint damage in RA. This blockade suppresses downstream inflammatory signaling pathways that would otherwise activate immune effector responses and perpetuate chronic inflammation. Unlike broader immunomodulators, adalimumab exhibits high specificity for TNF-α and does not significantly bind other cytokines such as lymphotoxin or interleukins, which contributes to its focused pharmacological profile. In RA, TNF-α is essential for promoting osteoclastogenesis through upregulation of nuclear factor-κB ligand (RANKL) receptor activator, resulting in enhanced bone resorption and cartilage destruction. By neutralizing TNF-α, adalimumab reduces RANKL-mediated osteoclast activation, thereby limiting structural joint damage. TNF-α inhibition also decreases matrix metalloproteinase expression, further protecting joint integrity **.** Recent advances in antibody engineering and pharmacogenomic profiling continue to refine the clinical use of TNF-α inhibitors, including adalimumab, enhancing binding characteristics and informing personalized therapy through biomarker stratification**.** These developments support ongoing efforts to optimize therapeutic efficacy and minimize immunogenicity in patients receiving long-term biologic treatment.

II) Antagonist of Interleukin - 6 (IL-6) Receptor

Tocilizumab

An antagonist of interleukin-6 (IL-6) is Tocilizumab is an monoclonal antibody and a humanized antibody and is a well-researched drug in rheumatoid arthritis. An essential part of rheumatoid arthritis is played by the pleiotropic pro-inflammatory cytokine IL-6, which is important in immune regulation, persistent inflammation, and joint destruction. It works by attaching itself to the IL-6 receptor (IL-6R) and then binding to the signal-transducing protein gp130, to activate Janus kinase/signal transducer and activator of transcription (JAK/STAT) is one of the example of intracellular signaling pathway.

Signaling IL-6 takes place in two ways: classical signaling on cellular IL-6R that is bound by membrane-bound IL-6 on select cells and trans-signaling on cells through soluble IL-6R which allows IL-6 activity to be expressed on a broader range of cells as gp130 is ubiquitously expressed. Tocilizumab selectively attaches to membrane-bound IL-6 receptors that is soluble, which inhibits the connection between the receptor and IL-6 and formation of the IL-6/IL-6R/gp130 complex of signaling. Tocilizumab prevents IL-6 pro-inflammatory and immune responses by blocking both classical and trans-, thus qualifying as an effective treatment in autoimmune disorders like rheumatoid arthritis and cytokine releases syndromes.

This inflammatory response is antagonistic in nature and controls the disease activity, limits the systemic inflammation and halts damage on the joints. Consequently, tocilizumab has a high clinical efficacy and an overall acceptable safety profile, which makes it a worthy of the consideration in the contemporary management of RA.

III) Selective T - Cell Co-Stimulation Inhibition

Abatacept

Abatacept is a specific antagonist of T-cell co-stimulation and a biologic disease-modifying antirheumatic drug used to treat rheumatoid arthritis. T-cells need two signals to be effectively activated: one is antigen recognition via T-cell receptor and the other one is a co-stimulatory relationship between antigen-presenting

cells' CD80/CD86 and T cells' CD28. Without this additional signal, the T cells are in an inactive state and cannot trigger inflammatory immune responses.

Abatacept is a recombinant, bisulfated, non-glycosylated fusion protein made up of cytotoxic T- lymphocyte-associated antigen-4 (CTLA-4) extracellular domain which is covalently complexed with a modified human IgG1 Fc region. Since the CTLA-4 is more likely than CD28 to bind CD80 and CD86, abatacept is a competitive inhibitor of interaction between antigen-presenting cell-surface receptors and CD28. This blockade reduces T-cell growth by preventing full T-cell activation and a reduction of the release of pro-inflammatory cytokines.

Interfering with early immune activation, abatacept indirectly affects the activity of other immune cells, such as macrophages, and monocytes, which leads to reduced inflammation and autoantibody production. In this specific antagonistic mechanism, abatacept has demonstrated positive effects in decreasing both disease activity and joint destruction, and the safety profile is positive, which makes it an essential therapeutic option in the contemporary rheumatoid arthritis treatment.

IV) Suppression of The JAK-STAT (Janus Kinase-Signal Transducer and Activator of Transcription) Pathway

Tofacitinib

Tofacitinib is an orally-delivered small molecule inhibitor that is (JAK) pathway inhibitor for rheumatoid arthritis. It mainly blocks JAK1,JAK3, and somewhat JAK2 and interferes with JAKsignaling over JAKSTAT signaling in response to several pro-inflammatory cytokines. Usually, cytokine binding stimulates JAKs and results in the phosphorylation and transcription of genes that cause immune stimulation and inflammation.

Tofacitinib inhibits interleukin- 2, 4, 7, 15 and 21 signaling relying on the common 7-chain receptor, such as interleukins-2, 4, 7, 15 and 21, which are required by T-cells and natural killer cells. It also decreases cytokine signaling including IL-6 and interferons leading to decreased inflammatory mediator synthesis and leukocyte activation in the synovium. The result of this general suppression of cytokine pathways includes successful disease activity control, decrease of synovial inflammation, and delaying of joint damage. Because of its potent efficacy, quick activation of appearance, and tolerable safety profile, tofacitinib has gained a significant role in the modern rheumatoid arthritis treatment.

Therapeutic Drug Monitoring (TDM)

Why TDM is necessary for Biologicals ?

Rheumatic diseases are common, they affect a population at approximately 3 percent and were formerly quite debilitating. The introduction of the so-called medications that alter rheumatiod arthritis. In particular, (TNFi), has significantly enhanced patient outcomes. Nevertheless, it does not always respond in the first instance or maintain the effectiveness of the treatment with time, typically as a result of low drug levels in the serum or the development of anti-drug antibodies, whereas others fail to continue the treatment because of some adverse events. Modifications in treatment are usually of an empirical nature, however, TDM involving the measurement of drug troughs and anti-drug antibodies has become a method of maximizing therapy . TDM could be applied reactive to cause treatment changes in patients who lost their response or proactive to avoid relapse or overtreatment in patients who are in remission.

In case of rheumatoid arthritis, therapeutic drug monitoring plays an crucial part in maximizing the dosage, improving the responsiveness to therapy, and preventing adverse drug reactions, particularly with biologic and targeted therapy.

The table below presents specific TDM parameters in the case of popular agents that are utilized in management.

S.no	Parameters	Adalimumab	Tocilizumab	Abatacept	Tofacitinib
1.	Indications	ulcerative colitis, Rheumatoid arthritis, plaque psoriasis, chron's disease, psoriatic arthritis, ankylosing spondylitis,	From systemic juvenile idiopathic arthritis to moderate to severe rheumatoid arthritis, gaint cell arteritis, cytokine release syndrome.	Psoriatic arthritis, polyarticular juvenile idiopathic arthritis, and moderately severe rheumatoid arthritis.	Rhematoid arthritis, psoriatic arthritis, ulcerative colitis.
3.	Mechanism of action	Adalimumab is an entirely human IgG1 monoclonal antibody indicated for psoriatic arthritis, rheumatoid arthritis, plaque psoriasis, and ankylosing spondylitis. It specifically targets and neutralizes TNF-α, blocking its receptor binding and thereby suppressing inflammation, limiting joint damage, and improving clinical outcomes.	A humanized IgG1 monoclonal antibody is called tocilizumab. used in moderate to severe rheumatoid arthritis. It inhibits inflammatory activity by binding to membrane-bound and soluble IL-6 receptors, thereby inhibiting IL-6 dependent signaling and reducing disease activity and joint destruction.	A CTLA-4-Ig fusion protein called abatacept is used to treat rheumatoid arthritis. and psoriatic arthritis. It downregulates immune activation by attaching itself to antigen-presenting cells' CD80/CD86, blocking CD28-mediated T-cell co stimulation and thereby reducing inflammatory immune responses.	Tofacitinib is an orally administered small-molecule agent used in RA and other autoimmune conditions. It selectively inhibits JAK1 and JAK3, interrupting the JAK–STAT pathway and decreasing cytokine-driven inflammation and disease progression.
4.	Bioavailability	64% following subcutaneous administration.	48 - 80% (higher with SC 162mg vs.lower doses)	78 – 80 % (SC or IV)	74 % oral
5.	Absorption	Slow lymphatic uptake after SC injection, peak level achieved in 2-7 days.	Slow after SC injection nonlinear pharmacokinetics.	SC absorption with measurable steady state after weeks	Rapid cmax 0.5- 1 hour after oral dose.
6.	Distribution	predominantly intravascular and extracellular compartments.	limited distribution approximates extracellular fluid.	Primarily intravascular/ extracellular (large biologics)	moderate 87 liters
7.	Protein Binding	Minimal	minimal data specific typical of large monoclonal antibodies molecules.	not specifically defined (large proteins)	40%
8.	Volume of distribution	~5-6 L	~6-7 L	0.07 L/kg (≈ 5–8 L in adults)	~87 L (Adults ≥18 Years)
9.	Metabolism	Proteolytic degradation into peptides and amino acids.	Proteolytic catabolism like other IgG molecules.	proteolytic catabolism	Hepatic through CYP 3A4 (major) and CYP2C19(minor)
10.	Route of elimination	Reticuloendothelial catabolic pathways.	reticuloendothelial system.	Reticuloendo-thelial system	hepatic metabolism- 70% and renal excretion- 30%

11.	Clearance	Slow, increased in the presence of anti-adalimumab antibodies.	Nonlinear, target mediated elimination	Linear PK increases with body weight	Moderate, first order kinetics
12.	Elimination half life	Approximately 10- 20 days.	11- 13 days depending on dose/ regimen	13 -16 days	3-6 hours
13.	Optimum sampling time (Peak and trough levels)	trough concentration measured immediately before the next scheduled dose. Peak 2-7 days, trough add day 14 with biweekly dosing	trough pre dose for exposure assessment. peak after days post dose, trough before next dose.	Trough level proportional to steady state exposure. peak after dosing period trough at end of dosing interval.	Not typically used for TDM, through if PK profiling. C max 0.5-1 h; trough at 12 h (BID dosing)
14.	Therapeutic range	Trough therapeutic level ≥ 3.5–4.0 mg/L	trough levels > ~5 µg/mL	trough ~10 microgram/ml associated with optimal DAS28 response	no defined TDM range dose guided clinically
15.	Maintenance dose	Adults (≥18 years): 40 mg . Weight-based dosing (mg/kg) is used in children	Adults(≥18 years): I.v:8mg/kg every four weeks; **Pediatric patients (JIA):** IV: 8–12 mg/kg depending on body weight	10mg/kg Iv monthly Pediatric patients (JIA): IV: 10 mg/kg at specified intervals	Adults(≥18 years): 5 mg orally twice daily
16.	Loading dose	not routinely recommended	Not routinely required.	IV: 500 mg for <60 kg; 750 mg for 60–100 kg; 1000 mg for >100 kg	Not applicable treatment begins directly with the maintenance dose.
17.	ADR	serious and opportunistic infections, injection- site reactions. Demyelinating disorders, lupus like syndrome.	infection risk, neutropenia, elevated LFT'S, GI symptoms.	Infections, headache, Hypotension, Chills, UTI's	Infections, thrombosis risk, cytopenia
18.	Drug-drug interactions	Serious infections are a risk associated with other biologic DMARDs (such as anakinra, abatacept, and other TNF inhibitors).	Warfarin, statins, oral contraceptives: Tocilizumab speeds up CYP450 enzymes, so these drugs may work less. Tocilizumab can lower the effect of many CYP450-metabolized medicines.	TNF inhibitors or other biologics → ↑ serious infection risk	Immunosuppressants (biologic DMARDs, azathioprine, cyclosporine) → ↑ infection risk
19.	Drug-disease interactions	contraindicated in active infections, untreated tuberculosis and demyelinating disease.	active infection, liver impairment caution	Active infection caution.	hepatic and renal impairment adjustments required

20.	Monitoring therapy	trough drug levels, anti drug antibodies inflammatory markers (CRP/ ESR) and clinical disease activity.	clinical response, CRP/ ESR, CBC, liver enzymes	Clinical disease activity, Baseline: TB, Hepatitis screening	CBC, LFT'S, lipid profile, screening: TB, Hepatitis

Conclusion

Modern medicine and breakthroughs in immunology have led to a better understanding of rheumatoid arthritis. Even though it is still a chronic autoimmune inflammatory illness that can lead to joint damage and disability, its management has altered dramatically as a result of early diagnosis and better treatment techniques. Certain inflammatory pathways like TNF-a and IL-6 are targeted by contemporary treatments such biologic medications and JAK inhibitors, which serve to reduce inflammation and halt the progression of disease. Many patients are able to attain better illness control and a higher. Quality of life with the use of therapeutic medication monitoring, individualized treatment plans, and increased awareness. As a result, ongoing research and cutting-edge tailored treatments are crucial to the current treatment of rheumatoid arthritis.

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