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COMPARATIVE ANALYSIS OF AZATHIOPRINE AND METHOTREXATE IN RHEUMATOID ARTHRITIS: SAFETY, COMPLIANCE, EFFICACY AND COST EFFECTIVENESS

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ABSTRACT
Rheumatoid arthritis is a habitual seditious condition that occurs at joints, blood vessels and bones which leads to the physical incapability and internal illness. It caused by vulnerable factors and microbial factors. The treatment for Rheumatoid arthritis is done by NSAIDs [non-steroidal anti-inflammatory medicines], DMARDs [Disease modifying anti-rheumatic medicines], glucocorticoids, natural agents- monoclonal antibody remedy. DMARDs are the agents that performs major part in repression of the condition RA. The medicines like cyclosporine, azathioprine, methotrexate, hydroxychloroquine were involved in remedy. The information is collected through colourful journals and papers of arthritis from PubMed and Google scholar. The azathioprine [AZA] and Methotrexate [MTZ] both are immunomodulatory [immunosuppressive] agents that are used in colourful bus vulnerable conditions treatment. Azathioprine is a purine analogy which intrude with protein conflation and cell proliferation and reduces RA. Methotrexate is a medicine which is of same class intrude with DHFR [di- hydro folate reductase] reduce cell proliferation, hyperactive vulnerable response and active macrophages. Still the medium is analogous, but its adverse effect, patient compliance, safety and cost factors differs. Azathioprine considered to be most patient compliable, effective, safe and cost effective as compared to methotrexate.

KEYWORDS: Rheumatoid arthritis, NSAIDs, DMARDs, Glucocorticoids, Biological agents, Azathioprine[AZA], Methotrexate[MTZ], compliance, effective, safe and cost effective.

INTRODUCTION
Rheumatoid arthritis [RA] is a habitual and systemic seditious complaint that causes inflammation in joints, blood vessels and napkins. It causes severe pain and rupture of bones which leads to physical illness. Rheumatoid arthritis is treated with further generally with NSAIDs [non-steroidal anti-inflammatory medicines], glucocorticoids, DMARDs [Disease modifying anti-rheumatic medicines] immunosuppressants, antibiotics and Monoclonal antibody medicines. The most common immunomodulatory agent used in RA is methotrexate [MTZ]. The medicine is specified grounded on the conditions of case. Azathioprine [AZA] is an immunomodulatory drug extensively used in the treatment of autoimmune complaint, seditious bowel complaint. My composition is grounded on how AZA acts on RA and its compliance.[1]

EPIDEMIOLOGY, FREQUENCY AND PATHOPHYSIOLOGY
Arthritis is a group of conditions that beget inflammation in the joints, performing in pain, stiffness, and dropped range of stir. It's a major cause of disability worldwide, affecting individualities of all periods but is particularly current in aged grown-ups. The two most common types

are osteoarthritis [OA] and rheumatoid arthritis [RA], although other forms like psoriatic arthritis and gout are also significant. Arthritis is one of the leading causes of disability worldwide. The global frequency varies by region, population, and the specific type of arthritis. Osteoarthritis [OA] is the most common form, affecting an estimated 10 – 15 of the global population over the age of 60. Rheumatoid arthritis [RA] is less common, affecting roughly 0.5 – 1 of the global population, but it has significant long- term health impacts. Psoriatic arthritis affects roughly 0.5 – 1 of people, frequently in confluence with psoriasis. Gout is current in 2 – 4 of the population in some Western countries, with increased rates observed in men. The threat of developing arthritis increases with age. Osteoarthritis [OA] is most generally seen in people over the age of 50, and the frequency increases with advancing age. Rheumatoid arthritis [RA] generally manifests in early majority to middle age [periods 30- 60], but can affect people at any age. Rheumatoid arthritis [RA] is more common in women [roughly 2- 3 times more likely than in men]. Osteoarthritis [OA] affects both men and women, but men are more likely to develop OA before in life [frequently in the hipsters joint], while women tend to develop it latterly, especially in the knee joint. Gout is more common in men, with its onset generally being in middle age or latterly. Socioeconomic and Geographic Variability Prevalence rates of arthritis vary across different regions and socioeconomic groups. Advanced rates of osteoarthritis are seen in bucolic nations, while other forms, similar as rheumatoid arthritis, are more current in certain populations, like those of European or Native American descent.[2]

PATHOPHYSIOLOGY

Arthritis pathophysiology involves intricate mechanisms that affect in common inflammation and degeneration, driven by vulnerable system dysfunction and oxidative stress. Deregulated vulnerable responses contribute to habitual inflammation and joint pain. Crucial pro-inflammatory cytokines, including TNF, interleukin- 1, and interleukin- 6, play vital places in promoting inflammation and towel breakdown by retaining vulnerable cells to the joints, enhancing the seditious process. Microbial and environmental factors also contribute by dismembering DNA and converting protein citrullination. These altered citrullinated proteins spark B cells, T cells, macrophages, and endothelial cells, amplifying the vulnerable response. B and T cell activation triggers further vulnerable exertion, while macrophages release pro-inflammatory cytokines similar as TNF and interleukins, aggravating towel and common damage, including fluid build-up. Endothelial cells gain, and relations among vulnerable cells, cytokines, and endothelial microglial cells affect in towel thickening and common inflammation, hallmark features of arthritis.[1, 2]

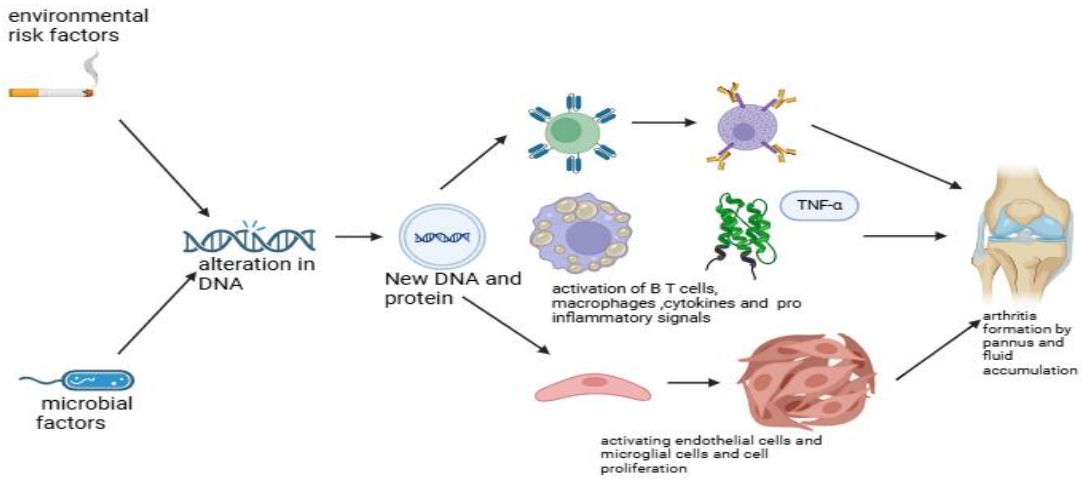

Fig. 1: Pathophysiology of arthritis.

SYMPTOMS, CURATIVES AND CURRENT MEDICINE REMEDY

Rheumatoid arthritis [RA] symptoms reflect its nature as a systemic seditious condition. Common early signs include fatigue, prolonged morning stiffness, and pain that improves with exertion — features that can help distinguish RA from non-inflammatory arthritis types like osteoarthritis. In discrepancy, osteoarthritis generally involves minimum morning stiffness but worsening pain with exertion.[3,4]

CURRENT TREATMENT

The pharmacologic curatives for RA are outlined in the table below. As RA is a seditious condition, original treatment frequently involves specifics that reduce inflammation, similar as non-steroidal anti-inflammatory medicines [NSAIDs] and glucocorticoids. These specifics give rapid-fire relief from pain and swelling associated with RA. Also, disease modifying anti-rheumatic medicines [DMARDs] are generally used and include options like methotrexate, hydroxychloroquine, sulfasalazine, and more lately, leflunomide.[3,5]

Table 1: Drugs used in treatment of arthritis.

Category	Examples
NSAIDs	Aspirin, ibuprofen, nimesulide, piroxicam, valdecoxib, etorcoxib, tofacitnib, Febuxostat
Glucocorticoids	Prednisolone, methyl prednisolone
DMARDs	Methotrexate, hydroxychloroquine, sulfasalazine, Leflunomide
Biological agents	
Anti TNF-alpha	Infliximab, etanercept, adalimumab
IL-1 inhibitors	Anakinra
Co-stimulation blockers	Abatacept
B cell targeted therapies	Rituximab

NSAIDs

Non-steroidal anti-inflammatory medicines [NSAIDs] are generally used to manage the pain, inflammation, and stiffness associated with RA. Their efficacy relies on inhibiting cyclooxygenase [COX] enzymes, particularly COX- 2, which plays a significant part in inflammation by producing prostaglandins E2 and I2. These prostaglandins help reduce inflammation. Still, NSAIDs are associated with implicit adverse goods, including hepatotoxicity, renal toxin, cardiovascular pitfalls, and gastric ulcers.[6]

GLUCOCORTICOIDS

Glucocorticoids act by cranking glucocorticoid receptors, which promote the product of proteins like tristetraprolin, annexin A1, and NF- κB impediments. Annexin A1, in particular, regulates phospholipase A2 in the arachidonic acid pathway. Glucocorticoids inhibit these enzymes, reducing seditious signals and pannus conformation, thereby mollifying RA symptoms. Still, their adverse goods can be significant, including rotundity, cardiovascular diseases, hyperlipidaemia, and skin infections.[4,7]

DMARDs

Disease modifying anti rheumatic medicines [DMARDs] are the foundation of RA remedy. They inhibit cytokines, reducing seditious responses, converting apoptosis, and suppressing rib nucleotide uredines monophosphate [rump], which limits cell proliferation while promoting anti-inflammatory and immunomodulatory goods. Still, DMARDs may beget gastrointestinal issues [nausea, puking, ulcers, and appetite loss], hepatotoxicity, and teratogenicity in pregnant women, malice, alopecia, and anaemia.[4,8]

NEW DRUG CURATIVES

Recent advances in RA treatment include medicines like leflunomide, etanercept, adalimumab, infliximab, anakinra, and immunosuppressants similar as methotrexate, certolizumab, and golimumab. These curatives offer targeted approaches to managing RA and its symptoms.[5]

HYPOTHETICAL APPROACH

Azathioprine [AZA] is an immunosuppressant and purine analogue extensively used to treat colourful autoimmune conditions, seditious bowel conditions, organ transplant rejection, and order diseases. Given that rheumatoid arthritis [RA] is an autoimmune complaint, AZA can be effective in its operation due to its anti-inflammatory and immunomodulatory parcels. Azathioprine [AZA] can serve as a volition to methotrexate in the operation of rheumatoid arthritis [RA], potentially perfecting patient compliance and reducing the adverse goods generally associated with methotrexate. Its immunosuppressive and anti-inflammatory parcels make it a feasible option for cases who may not tolerate methotrexate well.[9,10]

METHODOLOGY

The data gathered from PubMed and Google Scholar was collected and synthesized into a comprehensive report.

Rheumatoid Arthritis

Rheumatoid arthritis [RA] is a long- term autoimmune and systemic seditious condition characterized by symmetrical common towel damage, eventually performing in immobility. The vulnerable system's activation triggers the release of seditious cytokines in the synovial fluid, leading to pannus conformation and accelerating the breakdown and destruction of the synovial membrane, which distorts and damages joints. Colourful suppositions have been suggested to explain the origin and build-up of lipids in normal synovial fluid and the factors contributing to their elevated situations in RA synovial fluid, including.[11]

1. The semi-permeability of the synovial membrane.
2. Active and picky transport of lipoproteins into the synovial membrane.
3. Declination of synovial cells.
4. Original lipid conflation.
5. Phospholipase- driven phospholipid development in synovial fluid.
6. Habitual inflammation- convinced blockage of venous or original lymphatic drainage.

SELECTION CRITERIA

The specifics used for treating rheumatoid arthritis [RA] include those listed over. Operation remedy has involved the use of antihistamines, platelet aggregation impediments, and anti-Alzheimer's medicines. Among Disease- Modifying Anti rheumatic medicines [DMARDs], the immunosuppressant Methotrexate [MTZ] was preliminarily the most generally used for RA. Still, it's associated with significant adverse goods

and poor case compliance. Azathioprine, another medicine from the same class, has been observed in clinical studies to have smaller adverse goods and better case compliance. Its parcels and goods suggest that it may also be an effective, safe, and tolerable option for RA treatment.[12]

IMMUNOSUPPRESSANTS

Immunosuppressants are medicines or substances that reduce or weaken the vulnerable system's exertion. They're primarily used to help organ transplant rejection, treat autoimmune diseases, and manage seditious conditions by moderating the vulnerable response.[13, 14]

TYPES OF IMMUNOSUPPRESSANTS

Immunosuppressants are categorized based on how they work to suppress the immune system.[15]

1. Calcineurin Inhibitors

Action: Block calcineurin, an enzyme crucial for T-cell activation, leading to reduced production of interleukin-2 [IL-2], a key factor in T-cell proliferation.[16, 17]
Examples: Cyclosporine, Tacrolimus

2. Antiproliferative and Antimetabolic Agents

Action: Disrupt DNA synthesis, hindering the growth and division of rapidly multiplying immune cells, particularly T and B lymphocytes.[8, 18, 19]
Examples: Azathioprine, Mycophenolate mofetil [MMF], Methotrexate

3. mTOR Inhibitors

Action: Target the mammalian target of rapamycin [mTOR] pathway, which is essential for the growth and proliferation of T and B cells.[20-22] Examples: Sirolimus [Rapamycin], Everolimus.

4. Glucocorticoids

Action: Suppress inflammation and immune activity by reducing cytokine production and T-cell activation.[4, 7, 8]
Examples: Prednisone, Methylprednisolone, Dexamethasone.

5. Biologic Agents [Monoclonal Antibodies and Fusion Proteins]

Action: Specifically target components of the immune system, such as cytokines, cell surface markers, or immune checkpoints.[23,24]
Examples: Basiliximab [targets IL-2 receptors], Rituximab [targets CD20 on B cells], Belatacept [blocks CD80/86]

6. Alkylating Agents

Action: Disrupt DNA replication, affecting immune cells' ability to divide and function.[25] Examples: Cyclophosphamide, Chlorambucil.

7. Janus Kinase [JAK] Inhibitors

Action: Block the JAK-STAT signalling pathway, which is involved in cytokine-driven immune responses.[26,27]
Examples: Tofacitinib, Baricitinib.

8. Other Immunosuppressants

Anti-thymocyte Globulin [ATG]: Polyclonal antibodies that target T cells.[28]
Leflunomide: Inhibits pyrimidine synthesis, limiting lymphocyte proliferation.[29] Hydroxychloroquine: Alters immune cell activity, commonly used in conditions like lupus.

ANTIPROLIFERATIVE AGENTS

Antiproliferative agents are immunosuppressive drugs that function by halting the growth and division of cells, particularly T and B lymphocytes, which are critical to the immune response. These medications are commonly employed in organ transplantation and the treatment of autoimmune disorders to suppress overactive immune activity.[30, 31]

MECHANISM OF ACTION

these agents interfere with cellular mechanisms required for DNA synthesis and cell division. By targeting rapidly dividing immune cells, they help limit their proliferation, thereby reducing immune-driven damage or the likelihood of organ rejection.[31, 32]

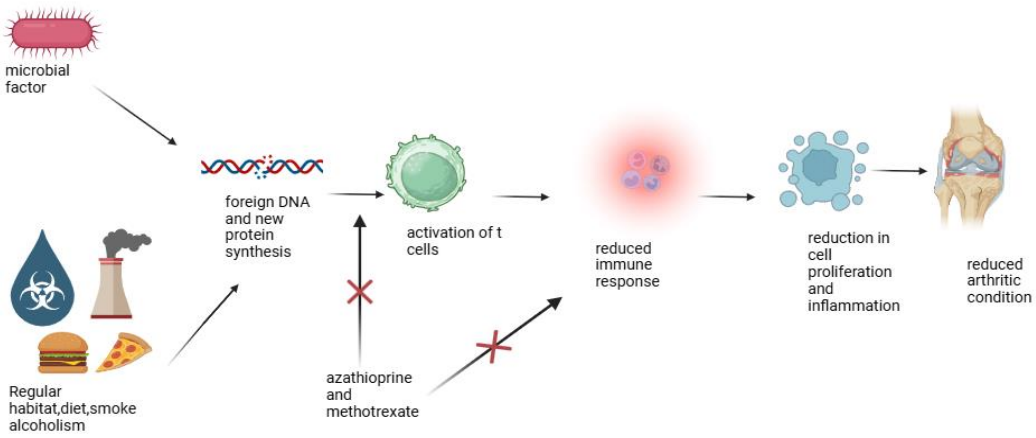

Fig. 2: drug pathway of anti-proliferative agents.

MECHANISM OF METHOTREXATE IN RA

Methotrexate [MTX] is a fundamental treatment for rheumatoid arthritis [RA] and other inflammatory arthritis. Its effectiveness stems from its ability to suppress immune function, decrease cytokine production, and manage inflammation, ultimately mitigating joint damage and relieving symptoms.[9,33,34]

1. Inhibition of Dihydrofolate Reductase [DHFR]

Mechanism: Methotrexate blocks DHFR, reducing tetra hydro folate [THF] levels. THF is critical for the synthesis of purines and pyrimidine's, essential for DNA and RNA production.[9,34]

Effect in RA: Suppresses proliferation of activated T and B lymphocytes involved in the autoimmune response. Reduces the expansion of inflammatory immune cells at the site of joint inflammation.[34]

2. Enhanced Adenosine Release

Mechanism: Methotrexate increases adenosine levels by inhibiting AICAR transformylase, leading to adenosine accumulation.[9,34]

Anti-Inflammatory Role of Adenosine

Binds to adenosine receptors [A2A] on immune cells. Inhibits neutrophils, macrophages, and dendritic cells. Reduces production of pro-inflammatory cytokines like TNF-α, IL-1, IL-6, and IFN-γ. Promotes anti-inflammatory cytokines such as IL-10.Effects on endothelial cells minimize vascular inflammation and neutrophil recruitment, reducing joint swelling and pain.[34]

3. Suppression of Pro-Inflammatory Cytokines

Mechanism: Methotrexate inhibits the production of key cytokines involved in RA pathogenesis.[35]

- **TNF-α**: Central to synovial inflammation and joint damage.
- **IL-1**: Promotes cartilage degradation and bone resorption.
- **IL-6**: Drives acute-phase inflammation and systemic effects like fatigue and anemia.

4. Modulation of T-Cell Activity

Suppresses inflammatory Th1 and Th17 cells, reducing their cytokine production. Enhances regulatory T cells, fostering immune tolerance and mitigating autoimmunity. Limits immune attacks on joint tissues.[36,37]

5. Reduction in Neutrophil Activity

Methotrexate reduces chemokine production, decreasing neutrophil infiltration into synovial tissues. Limits the release of enzymes and reactive oxygen species [ROS] responsible for joint damage and inflammation.[38]

6. Inhibition of Matrix Metalloproteinases [MMPs]

Methotrexate lowers the expression of MMPs, enzymes that degrade cartilage and extracellular matrix in RA. Slows down joint erosion and structural damage.[39]

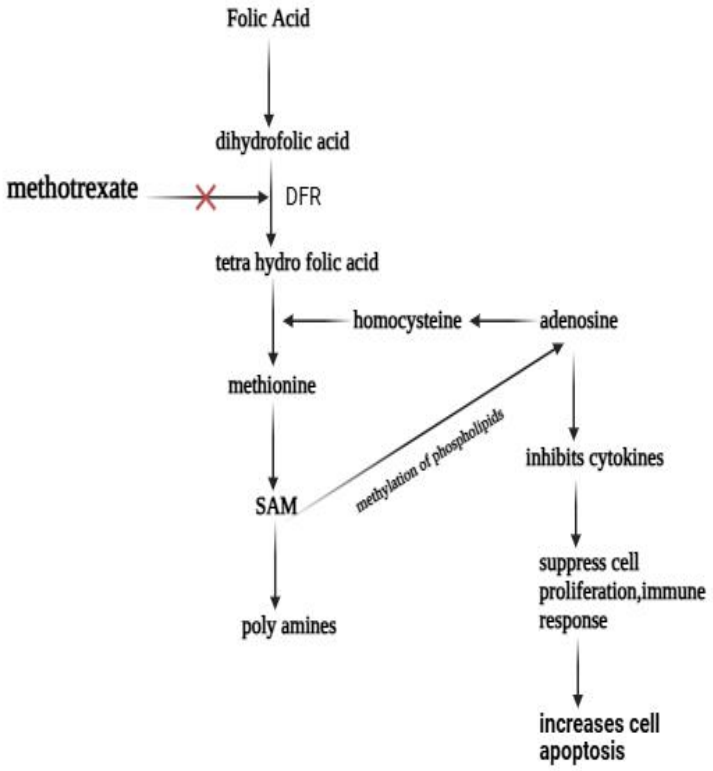

Fig. 3: Mechanism of Methotrexate.

MECHANISM OF AZATHIOPRINE IN RA

Rheumatoid arthritis [RA] and other autoimmune illnesses are frequently treated with the immunosuppressive medication azathioprine [AZA]. It works by limiting the growth of immune cells that fuel the autoimmune reaction, which lowers inflammation and keeps joint tissue from being harmed.[40]

Conversion of active form: Being a prodrug, azathioprine must undergo metabolism in order to become its active form. It is transformed into the active ingredient, 6-mercaptopurine [6-MP], in the body.[41]

Inhibition of Purine Synthesis: 6-MP prevents purines, which are crucial DNA building components, from being synthesized. 6-MP prevents the reproduction of rapidly dividing immune cells, especially T and B lymphocytes [which are essential for the immunological response], by preventing purine metabolism.[42]

Immunosuppressive Effects: The immune system is generally suppressed as a result of these immune cells' decreased proliferation. In autoimmune diseases like RA, when the immune system unintentionally targets healthy joint tissues, this is especially helpful.[43]

Reduction of Inflammation: Azathioprine lowers the generation of inflammatory cytokines by blocking immune cell function, including[such interleukins and TNF-α] that fuel the long-term inflammation and joint degeneration associated with RA.[44]

Effect on Disease Progression: Azathioprine may reduce the progression of rheumatoid arthritis by preventing the long-term damage to joints and tissues that can arise from an unchecked immune response.[45]

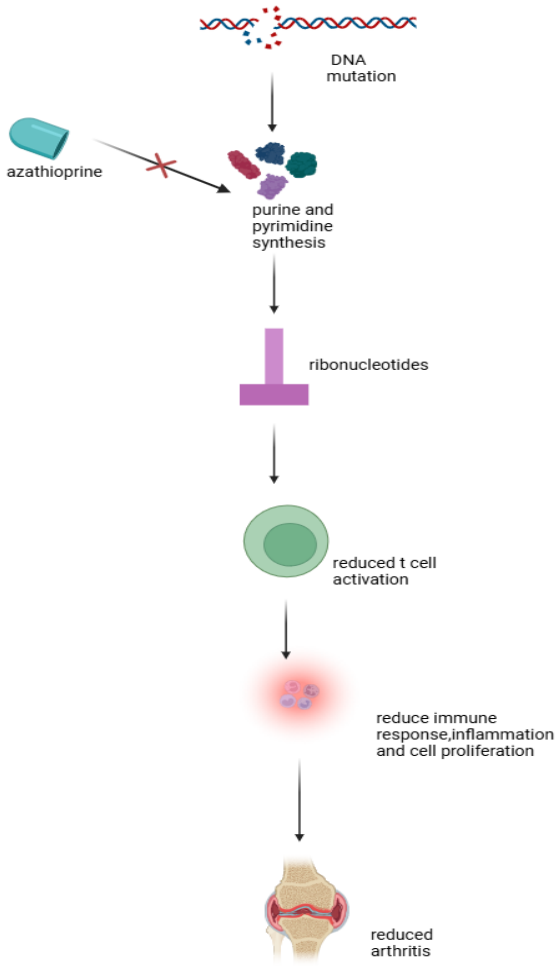

Fig. 4: Mechanism of Azathioprine.

COMPARISON OF ADR -METHOTREXATE VS AZA

Methotrexate is associated with a range of adverse effects, both common and serious. Common side effects include gastrointestinal issues such as nausea, vomiting, diarrhoea, and stomatitis [mouth sores]. Hematologic complications like bone marrow suppression may lead to anemia, leukopenia, and thrombocytopenia. Hepatic effects often involve elevated liver enzymes and, with prolonged use, a risk of hepatotoxicity or fibrosis.

Dermatologic reactions, including rash, alopecia, and photosensitivity, are also observed, alongside general symptoms like fatigue and malaise. Serious adverse effects, though less frequent, include pulmonary complications such as interstitial lung disease or methotrexate-induced pneumonitis, as well as increased susceptibility to infections due to immunosuppression. Neurotoxicity may manifest as headaches, dizziness, or, in rare cases, leuko encephalopathy. Methotrexate is highly teratogenic and contraindicated during pregnancy due to the risk of severe fetal harm. Additionally, high doses can lead to acute kidney injury, although this is less common in low-dose therapy.[12,46]

Azathioprine is associated with various adverse effects, ranging from mild to serious. Common side effects include gastrointestinal symptoms such as nausea, vomiting, diarrhoea, and abdominal pain, as well as hematologic issues like bone marrow suppression, which may result in leukopenia, anemia, and thrombocytopenia. Mild infections are also more likely due to the drug's immunosuppressive effects. Serious adverse effects include hepatotoxicity, which is less common compared to methotrexate, and hypersensitivity reactions that may present with fever, rash, and systemic symptoms. Rare but severe complications include acute pancreatitis and an increased risk of malignancies such as lymphoma, non-melanoma skin cancers, and others with prolonged use. Myelosuppression risk is heightened in patients with thiopurine methyltransferase [TPMT] deficiency. Immunosuppression from azathioprine also increases susceptibility to opportunistic infections. While generally considered safer than methotrexate during pregnancy, it should still be used with caution under medical supervision.[46-49]

Table. 2: Adverse effects of methotrexate and azathioprine.

Category	methotrexate	Azathioprine
Gastrointestinal	Common [nausea, stomatitis]	Common [nausea, diarrhoea]
Hepatotoxicity	Frequent; requires regular monitoring	Less common, but still a concern
Bone marrow	Suppression [dose-dependent]	Suppression [higher with TPMT deficiency]
Pulmonary	Rare pneumonitis	Rare, typically not lung-specific
Teratogenicity	High	Low to moderate
Malignancy	Mild increase	Increased risk of lymphoma
Special Risks	Pulmonary fibrosis, teratogenicity	Pancreatitis, hypersensitivity reactions

DISCUSSION

Methotrexate and azathioprine belong to the same class of drugs used to treat autoimmune diseases. While methotrexate has been widely used in rheumatoid arthritis [RA], azathioprine has not been as commonly utilized. Comparing the adverse effects and pharmacokinetics of both drugs reveals that azathioprine tends to have fewer side effects. Furthermore, studies on compliance show that azathioprine is better tolerated by patients. Safety data also indicate that azathioprine is safer than methotrexate. The combined therapy of these drugs is risk and contraindicated. Therefore, azathioprine could serve as a substitute for methotrexate in the treatment of RA.[50,51]

COI

There is no Conflict of Interest between the authors.

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