A complete review on Immunosuppressants Drugs

Garkhede M.B[1], Wankhare S.R[2],Vyas G.V[3], RawatS.S[4]
[1]*Student in Institute of Pharmacy Badnapur*
[2,3]*Assist professor in Institute of Pharmacy Badnapur*
[4]*Principal In Institute of Pharmacy Badnapur*

Abstract- This review will outline a number of immunosuppressive agents that are presently being explored in Experimental and clinical transplantation.(4) Immunosuppressant's are medicines or drugs that lower the body's capability to reject a transplanted Organ also known asanti- rejection medicines (1). This medicines are which inhibit cellular and humoral or both types of vulnerable responses, and have their Major use in organ transplantation and autoimmune conditions. This medicines employed to help colorful autoimmune conditions similar as glomerulonephritis, myasthenia Gravis, arthritis, lupus, rheumatoid arthritis, Crohn'sdisease (1). Immuno suppressants holds back the vulnerable system helping to prevent cell damage and inflammation. numerous medicines similar as steroids calcineurin impediments (cyclosporine- A, tacrolimus), antimetabolites, (Mycophenolate- mofetil, azathioprine), and mTOR impediments (sirolimus, everolimus) are used as Immunosuppressive agents (2). Different types of immunosuppressive specifics can be used for short and long term, depending on the situation. The Immunosuppressant drug are occasionally used in combination with birth specifics to Ameliorate response to induction remedy and to reduce the chance of antibody conformation and loss of the drug's effectiveness. Advances in immunosuppressant advancements in Short- and long- term issues in organ transplantation as well as a dropped prevalence of acute Rejection (4). The details of the different immunosuppressive medicines have been bandied in this overview.

Keywords: Immunosuppressant, autoimmune, specifics, transplantation.

INTRODUCTION

Type of Immuno Suppressant

There are 2 types of immunosuppressants

1. Induction medicines important antirejection drug used at the time of transplant(13). Induction agents include lymphocyte- depleting antibodies similar as rabbit antithymocyte Globulin, alemtuzumab, muromonab- CD3, rituximab, and bortezomib; lymphocyteNondepleting antibodies similar as interleukin 2 receptor antibodies; and other Discontinued or investigational agents similar as efalizumab and alefacept(15).

2. conservation medicines Antirejection specifics used for the long term(13).

There are generally 4 classes of conservation medicines Calcineurin Impediments Tacrolimus and Cyclosporine Antiproliferative agents Mycophenolate Mofetil, Mycophenolate Sodium and Azathioprine mTOR asset Sirolimus Steroids Prednisone. A brief discussion of some new and generally used immunosuppressive medicines used in autoimmune diseases and organ transplant has been presented in this review.

1. Cyclosporine(Cyclosporine A)

Cyclosporine was first delved as an anti-fungal antibiotic. Cyclosporine comes as an oral capsule, an oral result, eye drops, and an injectable form. Brand names Gengraf, Neoral, Sandimmune. Cyclosporine is an immunosuppressive agent used to treat organ rejection post-transplant. It's calcineurininhibitor. Cyclosporine is an 11amino acid cyclic peptide immunosuppressant that has revolutionized organ transplantation(20). It is insulated from the fungus Beauverianivea. Discovery and pharmacological development of cyclosporine was conducted by Jean Borel and colleagues in the 1970s[19].Discovered in the lab of Sandoz in Switzerland in 1972,cyclosporine (CsA) has since revolutionized transplant medicine. Approved for use by the FDA in 1983[21]. It also has use in certain other autoimmune diseases, treatment of organ rejection in kidney, liver, and heart allogeneic transplants, rheumatoid arthritiswhen the condition has not adequately responded to methotrexate[18]. cyclosporine is nephrotoxic. It is

taken orally or intravenously for rheumatoid arthritis psoriasis, Crohn's disease, nephrotic syndrome, and in organ transplants to prevent rejection.

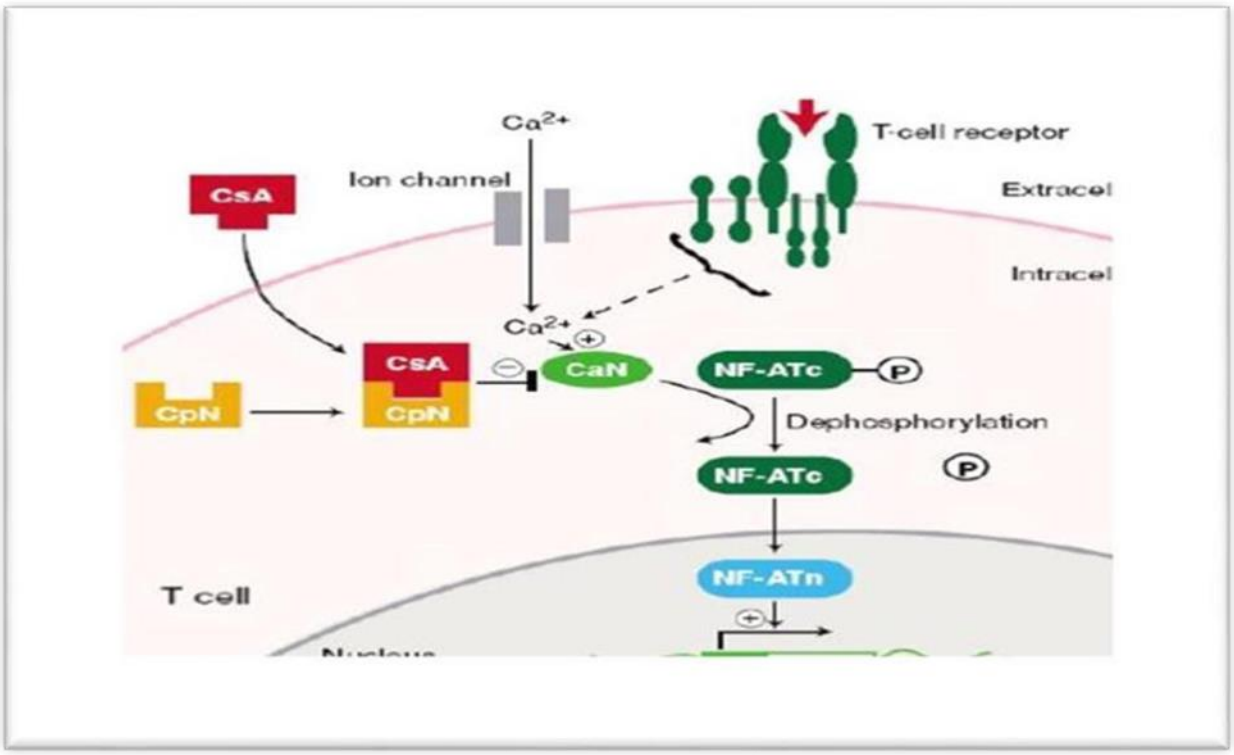

Fig: cyclosporine mechanism of action [77]

Mechanism of action:

Cyclosporine is a calcineurin inhibitor that inhibits T cell activation. Cyclosporine preferentially suppresses cell mediated immune Reactions, whereas Humoral immunity is affected to a far Lesser extent. Cyclosporine inhibits antigen triggered signal transductionin Tlymphocytes. After diffusing into the T 1 units, cyclosporine makes necessary to a cyclophilin to form a complex that makes necessary to calcineurin The latter is responsible for dephosphorylating NFATc. Because the cyclosporine-calcineurin complex cannot act this reaction, NFATc cannot move into the small group to give help to the reactions that are needed for the putting-together of a number of cytokines 2, including il2 attractive before use. The end outcome Is a drop in il-2 which is the first chemical thing causing reaction for increasing the no. of Tlymphocytes .It is most active when administered before antigen exposure.

Pharmacokinetic:

Cyclosporine is highly lipophilic and its oral absorption is slow and incomplete. Or given by intravenous infusion. In parenteral injection ethanol poly-oxyethylated castor oil is used as a vehicle and before IV injection this preparation must be further diluted in 0.9% NaCl solution or in 5% dextrose solution. Absorption is dependent on the presence of bile and there for prone to variability. Its oral bioavailability ranges from 10 to 89%. The drug is poorly absorbed, Variable and incomplete From gastrointestinal tract after oral administration with a bioavailability of about 30% (range 5% to 70%).Cyclosporine is extensively distributed in peripheral tissues. Its volume of distribution is 3 to 5 L/kg. Cyclosporin is widely distributed throughout the body. Peak concentrations in blood or plasma are reached in 1 to 8 hour. Cyclosporine (CsA) is extensively metabolized and primarily excreted in biles after dosing. Cyclosporine distribution in the blood is approximately 41 to 58% in erythrocytes, 33 to 47% in plasma, 5 to 12% in granulocytes, and 4 to 9% in lymphocytes. It is metabolized mainly in liver by the cytochrome-P450 3A (CYP-3A) enzyme to several

metabolites (25-30 metabolites) and most of the metabolites are excreted mainly through bile and little through urine (approx. 6%).

Clinical Uses:

Cyclosporine is used to prevent organ rejection in people who have received a liver, kidney, or heart transplant. Cyclosporine is useful for the short-term treatment of psoriasis and atopic dermatitis. Cyclosporine eye drops are used to increase tear production in patients who have a certain eye condition (eg, keratoconjunctivitis sicca).Cyclosporine suppresses the immune system in dogs, relieving symptoms of atopic dermatitis. Cyclosporine is also used to treat severe rheumatoid arthritis in patients who have failed treatment with methotrexate. Immunosuppression has been showed by this in transplant patients and in patients treated for dermatitis, peri-anal fistulas, keratoconjunctivitis sicca, faucitis and immune-mediated anemia.

Adverse effects:

Common side effects of cyclosporine are tremors, restlessness, stomach upset, nausea, cramps, diarrhea, headache, and changes in blood sugar, Unusual bleeding, Pale skin, Seizures, Rash, Purple blotches on the skin, Swelling of the hands, arms, and ankle.

Drug interaction:

Avoid eating grapefruit or drinking grapefruit juice when taking this medication. Consuming grapefruit products can increase the amount of cyclosporine in your body. Citrus juices especially GFJ and pomelo juice were found to significantly increase the plasma exposure of cyclosporine while orange juice did not exhibit anysignificant interaction with cyclosporine. Taking cyclosporine with certain antibiotics may lead to an increased risk of kidney damage like:

Ciprofloxacin,Gentamicin,Tobramycin,Trimethoprim/sulfamethoxazole,Vancomyci n.

The metabolism of 1,2-Benzodiazepine can be decreased when combined with Cyclosporine. also the risk or severity of renal failure and hypertension can be increased when Aceclofenac is combined with Cyclosporine. Cyclosporine andsirolimus should not be administered together, rather should be administered at separate time because sirolimus induces the cyclosporine associated nephrotoxicity whereas cyclosporine induces sirolimus associated hyperlipemia and myelosuppression .

1. Tacrolimus (FK506)

Tacrolimus, formerly known as FK506 or fujimycin is a macrolide antibiotic with immunosuppressive properties. Tacrolimus administration can be by oral, sublingual, topical, or intravenous (IV) route. Tacrolimus is used with other medications to prevent rejection of a kidney, heart, liver, or lung transplant.

This medicine may be used with steroids, azathioprine, basiliximab, or mycophenolate mofetil. Tacrolimus is a very strong medicine. Tacrolimus is a calcineurin inhibitor used to prevent organ transplant rejection and to treat moderate to severe atopic dermatits. It was discovered in 1984 from the fermentation broth of a Japanese soil sample that contained the bacteria Streptomyces tsukubaensis. Tacrolimus (FK506) is one of the calcineurin inhibitors that are widely used as immunosuppressive agents in organ transplantation. Oral tacrolimus is available in immediate-release and extended-release formulations.

Mechanism of action:

Peptide antibiotic binds to FK-binding protein inhibit calcineurin (cytoplasmic phosphatase)inhibit production of cytokines (Calcineurin regulates production of cytokines) Inhibits IL-1 and IL-2 receptor. Inhibits macrophage-T cell interaction andT cell responsiveness by decreasing T cell receptors response. Tacrolimus also inhibits transcription of genes which encode IL-3, IL-4, IL-8, GM-CSF and TNF-α, all of which are involved in the early stages of T-cell activation

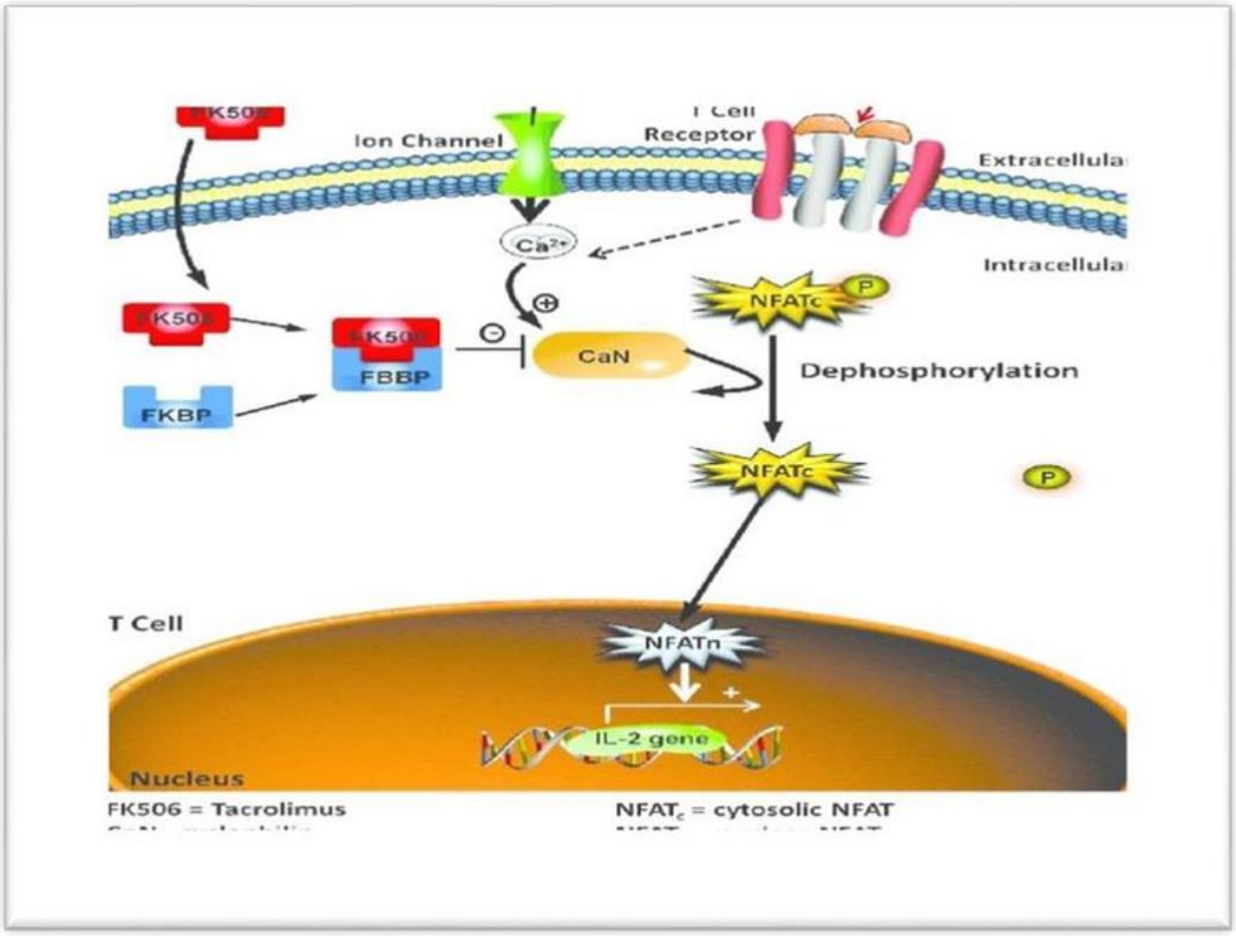

Fig 2: tacrolimus mechanism of action [78].

Pharmacokinetic:

Oral and intravenous preparations of tacrolimus are available in the market.more water soluble than cyclosporine.More predictable absorption.The terminal elimination half-life (t1/2beta) of tacrolimus is approximately 12 hours (with a range of 3.5 to 40.5 hours).Absorption of tacrolimus from the gastrointestinal tract after oral administration is incomplete and variable.the average bioavailability of tacrolimus is merely 25%, and it varies dramatically among individuals, ranging from 5 to 90%.the time of the meal also affected bioavailability.The absolute bioavailability in adult kidney transplant patients is 17±10%; in adults liver transplant patients is 22±6%; in healthy subjects is 18±5%.When given immediately after a meal, mean Cmax was reduced 71%, and mean AUC was reduced 39%, relative to the fasted condition.high levels of tacrolimus binding proteins in erythrocytes drive distribution. Aside from tacrolimus concentration, red blood cell distribution is dependent on several factors such as hematocrit, temperature and protein concentration.the mean disposition half-life is 12 hours and the total bodyclearance based on blood concentration is approximately 0.06 L/h/kg.the rate of absorption of tacrolimus is variable with peak blood or plasma concentrations being reached in 0.5 to 6 hours; approximately 25% of the oral dose is bioavailable.Tacrolimus is bound mainly to alpha1-acid-glycoprotein and to a lesserextent albumin as well as several other minor binding protein.tacrolimus is limitedby the low absorptivity of the drug, low plasma and blood concentrations, and the presence of metabolites and other drugs.tacrolimus is extensively bound to red blood cells, with a mean blood to plasma ratio of about 15; albumin and α1-acid glycoprotein appear to primarily bind tacrolimus in plasma.The absorption of tacrolimus occurs in the small intestine and is erratic and is decreased substantially by the presence of food.The metabolism of tacrolimus is predominantly mediated by CYP3A4 and secondarily by CYP3A5.6,7.the rate of the CYP3A enzymatic activities varies about 5 times from patient to patient,

and drugs that interfere withthe in vitro metabolism of tacrolimus in the liver also inhibit its small intestinal metabolism. Tacrolimus is a highly lipophilic drug and the distribution of tacrolimusis predominantly in the fatrich organs, such as adipose tissue. Tacrolimus is highly lipophilic and is excreted from the body after receiving extensive metabolism. Mostof metabolites and parent drug are excreted in feces.

Clinical Uses:

Tacrolimus is used for prevention of organ rejection in transplant patients. It has a wide range of biological activities including anti inflammatory and anti-oxidative properties. This medicine may be used with steroids, azathioprine, basiliximab, , mycophenolate mofetil. Tacrolimus is used together with other medicines in people who have had a heart, kidney, liver, or lung transplant.

Adverse effects:

Adverse effects requiring tacrolimus dosage adjustment include nephrotoxicity, neurotoxicity, alterations in glucose metabolism, and infection or susceptibility to malignancy. Headache, diarrhea, nausea/vomiting, upset stomach, loss of appetite, trouble sleeping, and numbness/tingling of the hands/feet may occur in over dose of tacrolimus.

Drug interaction:

Tacrolimus shows synergistic nephrotoxic effects when administered with cyclosporine. Antimicrobial agents that can have adverse effects on renal function may add to the nephrotoxicity of tacrolimus. Tacrolimus is potentially nephrotoxic and neurotoxic the likelihood of toxicity rises as blood levels of the drug increase. Conversely, drugs with the potential to induce the cytochrome P-450 3A system can reduce the levels of tacrolimus in the blood, leading to increased risk of acute rejection in transplant recipients. Avoid grapefruit juice while taking tacrolimus. Grapefruit and Grapefruit juice increase tacrolimus blood levels significantly leading to side effects like stomach pain, confusion, trouble passing urine or change in the amount of urine, dizziness, headache, mood changes, nausea, vomiting, tremor, yellowing o eyes or skin, or feeling unusually weak or tired. An interaction with topical tacrolimus is unlikely.

2. Cyclophosphamide:

Cyclophosphamide (Cytoxan; Cy) is an alkylating agent belonging to the group ofoxazaphosporines with cytotoxic and immunosuppressive activities Or chemotherapeutic agent with antineoplastic and immunosuppressive propertiesused for a broad range of indications. Cyclophosphamide is a medication primarily used in the management and treatment of neoplasms, including multiple myeloma, sarcoma, and breast cancer Also nitrogen mustard that exerts its anti-neoplastic effects through alkylation. As cyclophosphamide is in clinical use for more than 40 years, there is a lot of experience using this drug for the treatment of cancer and as an immunosuppressive agent for the treatment of autoimmune and immune-mediated diseases. It is used for patients, if they do not show any initial response to corticosteroids, or if the disease is refractory to corticosteroids.

Mechanism of action:

Cyclophosphamide is a type of nitrogen mustard drug which exerts its effects through the alkylation of DNA. Attachment of alkyl groups to DNA bases, resulting in the DNA being fragmented by repair enzymes in their attempts to replace the alkylated bases, preventing DNA synthesis and RNA transcription from the affected DNA.DNA damage via the structuring of cross-links(bonds between atoms in the DNA) which keeps from taking place DNA from being separated for putting- together or record-writing, and the discovery from examples of mispairing of the nucleotides leading to changes in structure. The recovery rate from cyclophosphamide is slow

Pharmacokinetic:

In most species, cyclophosphamide is rapidly absorbed, metabolized, and excreted. Cyclophosphamide can be administered by oral or intravenous route. Oraland intravenous administration of cyclophosphamide result in similar plasma concentrations. Cyclophosphamide is well absorbed after oral administration witha bioavailability greater than 75%.The time to peak plasma concentration of cyclophosphamide is 1-2 hours Injected cyclophosphamide distributed rapidly into 64% of body weight. Only 20% of injection cyclophosphamide was excreted intact inurine not more than that at any dose level .At least 80% of an administered dose of cyclophosphamide is eliminated by metabolism. Cyclophosphamide is principally excreted by the kidney. Cyclophosphamide undergoes metabolism to

several intermediates with alkylating activity. It is metabolized in liver by cytochrome-P450 (CYP450) enzymes system to aldophosphamide, phosphoramide mustard metabolites, which also have immunosuppressive property and anticancerous action. Cyclophosphamide is a prodrug that is activated in the liver by mixedfunction oxidase enzymes into 4-hydroxycyclophosphamide and which aldophosphamide; both are active forms of the drug. Metabolites of cyclophosphamide can act between, among with DNA and proteins ,coming out in the formation of adducts. The unchanged drug has an elimination half-life of 3 to 12hours. Acrolein is its another metabolite which causes bladder damage and alopecia. Bladder toxicity has been reported in 4-36 per cent of patients receiving this drug So, this drug combines with acrolein and detoxifies it, hence reducing thechances of baldder toxicity. MESNA is only found to be best to bladder irrigation alone.

Clinical Uses:

Cyclophosphamide is very effective in several types of vasculitis which were life threatening in the past. Cyclophosphamide is used to treat cancer of the ovaries, breast, blood and lymph system, and nerves (mainly in children) and it is also used for retinoblastoma (a type of eye cancer specially in children), multiple myeloma (cancer in the bone marrow), and mycosis fungoides (tumors on the skin).It is also indicated for the treatment of biopsy-proven minimal change nephrotic syndrome in pediatric patients. Plays key role in bone marrow transplantation. Cyclophosphamide is a medication primarily used in the management and treatment of neoplasms, including multiple myeloma, sarcoma.

Adverse effects:

Cyclophosphamide can cause myelosuppression leading to the development of sepsis and septic shock. Cyclophosphamide was associated with various toxicities, including liver toxicity, urotoxicity, cardiac toxicity, hematological, and non-hematological toxicities. Nausea and vomiting commonly occur with cyclophosphamide therapy. Avoid drinking grapefruit or Seville orange containing beverages. Do not eat grapefruit or Seville oranges while taking cyclophosphamide. Cyclophosphamide may cause infertility in both men and women who are treated with the medication. Overdose symptoms may include mouth sores, trouble breathing, fast heartbeats, rapid weight gain, stomach pain, or yellowing of your skin or eyes. Severe birth defects reported in several cases after cyclophosphamide given as little as 200 mg during pregnancy. The chances of toxicity can be decreased by keeping the course short and by administering it in theform of an injection every two to four weeks, rather than orally as a daily dose. Cyclophosphamide is an alkylating agent that can be given orally in dogs, with relatively little toxicity, occurs bone marrow suppression and sterile haemorrhagiccystitis.

Drug interaction:

Some products that may interact with this drug include allopurinol, chloramphenicol, chloroquine, digoxin, phenobarbital, phenothiazines, primidone, St John's wort, turmeric (curcumin), voclosporin.

4 .Azathioprine

Azathioprine is an immunosuppressive belonging to antimetabolite family whose action blocks purine synthesis that lowers the body's immune system used to prevent the body from rejecting a transplanted kidney. Also used to prevent renal transplant rejection, treat rheumatoid arthritis, Crohn's disease, and ulcerative colitis. Azathioprine is a pro-drug that is converted in vivo to 6-mercaptopurine (6MP), which is subsequently metabolized to the pharmacologically active 6thioguanine nucleotides (6-TGN).Azathioprine is one of the oldest immunosuppressive drugs and has been in use for over 25 yr in clinical transplantation. First synthesized in 1956 by Gertrude Elion, William Lange, and George Hitchings in an attempt to produce a derivative of 6-mercaptopurine with a better therapeutic index. It was one of the first drugs to be introduced into immunosuppression protocols for the prophylaxis of acute rejection in organ transplant recipients. Azathioprine (AZA) is approved by the Food and Drug Administration (FDA) for the therapy for the prevention of kidney transplant rejection.

Mechanism of action:

Azathioprine's mechanism of action is not entirely understood but it may be relatedto inhibition of purine synthesis, along with inhibition of B and T cells. Azathioprineis transformed into 6-mercaptopurine by glutathione. 6-Mercaptopurine is subsequently converted to thioinosinic acid and 6-thioguanine,

which are integrated into DNA and RNA, thus impairing their synthesis. Consequently, azathioprine inhibits the proliferation of lymphocytes. It also has cytotoxic action ondividing cells. It then inhibits purine synthesis. It has been suggested that for the IgG mediated disease, azathioprine is more effective whereas for IgM mediated diseasecyclophosphamide has greater efficacy.

Pharmacokinetic:

Azathioprine is well absorbed following oral administration with Tmax of 1-2 hours. After absorption, it undergoes metabolism in liver to the active metabolite. The half-life of azathioprine is about 10 minutes. The absolute oral bioavailability is estimated to be between 41% and 47%.it absorbed from the gastrointestinal tract and has a serum half-life of 0.2 to 0.5 hours and a biologic half-life of approximately24 hours. Azathioprine is 30% bound to proteins such as human serum albumin in circulation. Distributed in all tissues but does not cross the blood-brain barrier. In humans, azathioprine is readily absorbed from the gut. Following oral administration of 35S-azathioprine, 12% of the radioactivity is found in faeces as unabsorbed material, and 50% in the urine over 24 hours.

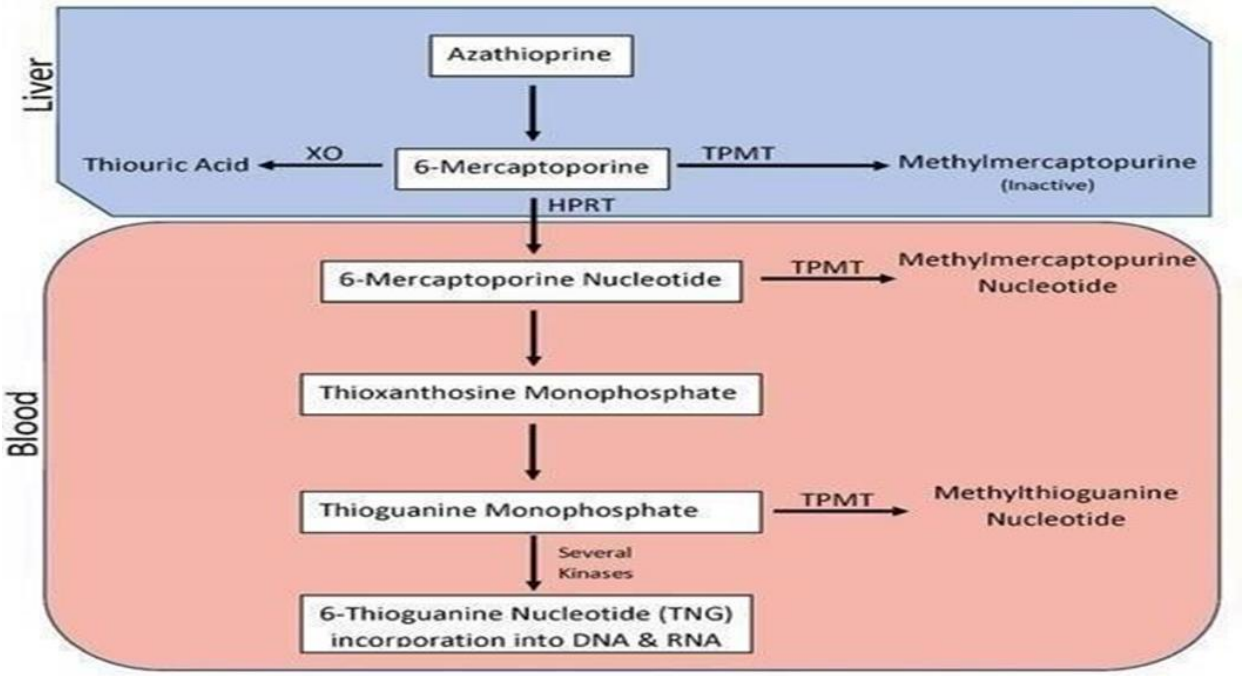

Fig 3 : Metabolism of Azathioprine [80].

Azathioprine is metabolized in the liver before becoming active. One metabolic pathway is through its conversion to 6-mercaptopurine, the active metabolite of 6mercaptopurine being 6-thioinosinic acid. Azathioprine also is metabolized by other pathways independently of 6-mercaptopurine.resulting in the inhibition of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and protein synthesis. Forty- five percent of the drug is excreted in the urine which are excreted by the kidneys.

Clinical Uses:

Azathioprine is now widely used as an adjunctive immunosuppressive agent in patients receiving solid- organ transplants, and in rheumatology, dermatology, and gastroenterology as an immunosuppressant and a corticosteroid-sparing agent. Azathioprine is used in dogs to treat inflammatory bowel disease, immune mediated anemia, colitis and skin disease; and Myasthenia Gravis. Azathioprine frequently is used with corticosteroids (prednisolone), with the goal of reducing the dose of both drugs and moving towards alternate day therapy. Azathioprine is safe for the fetus during pregnancy. Azathioprine and methotrexate have been used in combination to control severe rheumatoid arthritis. It is given at the dose rate of 2 mg/kg, orally, at interval of 24 hours.

Adverse effects:

Hematopoietic toxicity, including neutropenia, anemia, and thrombocytopenia, is the most common dose-limiting adverse effect. Nausea is the most frequent side effect. Fever, Fatigue arthralgias, bone marrow suppression causing pancytopenia, thrombocytopenia, leukopenia – there are reports of dose dependent, life-threatening cases. Liver adverse effects are the second most common. Increased incidence of neoplasia and opportunistic infections. Infants exposed to azathioprine in early pregnancy may be at a moderately increased risk of congenital malformations, specifically ventricular or atrial septal defects. Azathioprine, like other thiopurines, can also cause chronic liver injury andlong-term therapy has been linked to the development of portal hypertension andnodular regenerative hyperplasia.

Drug interaction:

Derivatives of benzoic acid can inhibit the TPMT pathway. Sulfasalazine and salicylic acid derivatives inhibit TPMT activity and can therefore augment azathioprine action. Some products that may interact with thisdrug are, febuxostat, past or present use of certain cancer drugs (such as cyclophosphamide, melphalan), other drugs that weaken the immune system/increase the risk of infection (such as rituximab, tofacitinib).Azathioprine should not be given to: Women of childbearing potential, Pregnant women, lactating mothers, who have shown hypersensitivity to the drug. The xanthine oxidase pathway is inhibited by Allopurinol. Patients receiving azathioprine and allopurinol concomitantly should have a dose reduction of azathioprine to approximately 1/3 to ¼ the usual dose. Use with Other Agents Affecting Myelopoesis: Drugs which may affect leukocyte production, including co-trimoxazole, may lead to exaggerated leukopenia, especially in renal transplant recipients.

5.Mycophenolate Mofetil (MMF)

Mycophenolate mofetil is an ester prodrug of the active immunosuppressantmycophenolic acid also a semi synthetic derivative of fungal antibiotic. Mycophenolic acid was initially discovered by Italian Bartolomeo Gosio in 1893 rediscovered in 1945 and 1968.first approval for the prevention of renal allograft rejection in 1995 .MMF is an inhibitor of inosine-5′-monophosphate and is able topreferentially inhibit B-cell and T-cell function. It is a noncompetitive, selective and reversible inhibitor of inosine monophosphate dehydrogenase, an important enzyme in the de novo synthesis of guanosine nucleotides in T and B lymphocytes.

Mechanism of action:

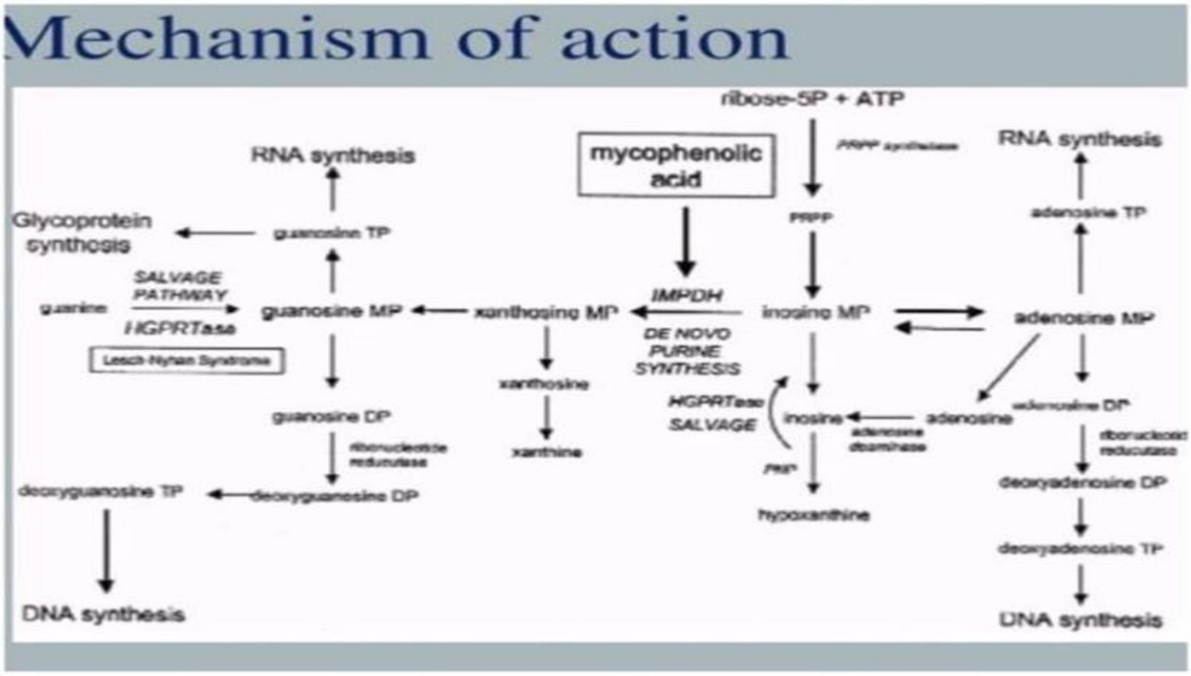

Fig 4:Mycophenolatem ofetil mechanism of action

This drug is rapidly converted mycophenolic acid, which inhibits inosine monophosphate dehydrogenase, an enzyme in the de novo pathway of Purine synthesis. This action suppresses both B and T lymphocyte activation and Lymphocytes are particularly susceptible to inhibitors of the de novo pathway because they lack the enzymes necessary for the alternative salvage pathway for purine synthesis. Drug inhibits both cell mediated and antibody mediated immunity and also decreases the production of cytotoxic T cells.

Pharmacokinetics:

Oral absorption of the drug is rapid and essentially complete. The mean absolute bioavailability of oral Mycophenolate Mofetil was 94%.Mycophenolate mofetil is rapidly absorbed in the small intestine. The average apparent half-life of mycophenolate mofetil is 17.9 (±6.5) hours after oral administration and 16.6 (±5.8) hours after intravenous administration.MPA is glucuronidated to the metabolite MPAG, which exhibits enterohepatic recirculation (EHC). MPA binds for 97% and MPAG binds for 82% to plasma proteins. After both oral and intravenous administration mycophenolate mofetil is entirely metabolized by liver carboxylesterases 1 and 2 to mycophenolic acid (MPA), the active parent drug. MPA is metabolized Principally by glucuronyl transferase to form the phenolic glucuronide of MPA (MPAG) which is not Pharmacologically active.it is metabolised primarily by glucuronidation and lacks nephrotoxicity, cardiovascular toxicity or diabetogenic potential, thus making it a suitable candidate for combination regimens. The volume of distribution of mycophenolate mofetil is 3.6 (±1.5) to 4.0 (±1.2) L/kg.Negligible amount of drug is excreted as MPA (<1% of dose) in the urine. 93% excreted in urine and 6% excreted in feces.

Clinical Uses:

Mycophenolate belongs to a group of medicines known as immunosuppressive agents which is used with other medicines (eg, cyclosporine, steroid medicine) to lower the body's natural immunity in patients who receive organ transplants (eg, kidney, heart, or liver).Solid organ transplants for refractory rejection. Steroid-refractory hematopoietic stem cell transplant patients and It canused alone and Combined with prednisone as alternative to cyclosporine or tacrolimus But not with azathioprine. In Combination therapy the dose of cyclosporine is reduced and therefore its toxicity. Also used in Rheumatoid arthritis,& dermatologic disorders.

Adverse effects:

Mycophenolate may cause pure red cell aplasia. Mycophenolate mofetil shows following adverse effect: asthma, herpes simplex infection, infection, metabolic acidosis, oral candidiasis, pleural effusion, respiratory tract infection, systemic cytomegalovirus disease, urinary tract infection, viremia, abdominal pain, acne vulgaris, anemia, anxiety, asthenia, back pain, cardiovascular disorder, chest pain, constipation, cough, depression, diarrhea, disorder of integument, drowsiness, dyspepsia, dyspnea, edema, fever, headache, hypercholesterolemia. In contrast to the other agents, side effects such as neurotoxicity, nephrotoxicity, infertility, hypertension and hyperglycemia are rarely seen with MMF. Diarrhea, vomiting, and inappetence are the most frequently reported In experimental study in dogs, doselimiting gastrointestinal (GI) adverse events (AEs) from MMF occurred at a dose of 60 mg/kg/day. MMF use during pregnancy is associated with an increased risk of malformations and first-trimester pregnancy loss.

Drug interaction:

Antivirals like acyclovir, Ganciclovir compete for tubular secretion, further increasing the concentrations of both drugs. Mycophenolatemofetil may decrease the effectiveness of oral contraceptives. Mycophenolate mofetil not be administered concomitantly with azathioprine or other immunosuppressant because both have the potential to cause bone marrow suppression and such concomitant administration has not been studied clinically. Cholestyramine decreases the plasma concentration of MPA by binding with free MPA in the intestine .

6.Sirolimus

Sirolimus is a natural macrocyclic lactone produced by the bacterium Streptomyces hygroscopicus, with immunosuppressant properties.it is also called known as rapamycin, It is antibiotic with potent immunosuppressive activity that is used alone or in combination with calcineurin inhibitors and corticosteroids to prevent cellular rejection after renal transplantation. Also it is a structural analogue of

tacrolimus but its action and side effects are somewhat different. Which was isolated from the soil of the Vai Atari region of Rapa Nui (Easter Island) and It was first isolated and identified as an antifungal agent with potent anticandida activity;however, after its potent antitumor and immunosuppressive activities were later discovered, it was extensively investigated as an immunosuppressive andantitumour agent. Sirolimus and tacrolimus bind to the same cytoplasmic FK-binding protein, but instead of forming a complex with calcineurin, sirolimus binds to mTOR (mammalian target of rapamycin), interfering with Signal Binding of sirolimus to mTOR blocks the progression of activated T cells from the G1 to the S phase of thecell cycle and, consequently, the proliferation of these cells. Unlike cyclosporine and tacrolimus, sirolimus does not affect IL-2 production but, rather, inhibit the cellular responses to IL-2.Only sirolimus was able to inhibit the proliferation of B cells and their differentiation into plasma cells.which leads to decreased quantity of immunoglobulins like IgM, IgG and IgA.

Pharmacokinetic:
Serolimus is absorbed rapidly after being administered orally.its maximum blood concentration occurs 1 to 2 h after oral administration, its bioavailability is low (around 15%), and its effective half-life allows a steady-state concentration to be reached at 5 to 7 days.sirolimus time to peak blood concentration, 1.4 +/- 1.2 hours; terminal half-life, 62 +/- 16 hours; oral dose clearance, 208 +/- 95 mL/h/kg; apparent oral steady-state volume of distribution, 12 +/- 5 L/kg; and blood/plasmaratio, 38 +/- 13.

Clinical Uses :
Sirolimus is used in combination with other medications to prevent rejection of kidney transplants. Sirolimus may also be used to treat a certain lung disease (lymphangioleiomyomatosis-LAM)It also Can be used together with cyclosporine to increases the activity of cyclosporine for organ transplanted patients. As replacement of cyclosporine if transplanted Patient developed cancer of skin or lips. In cynomolgus monkeys (Macaca Fascicularis), it causes prolongation of abdominal heart allograft survival.

Adverse effects:
Hyperlipidemia (elevated cholesterol and Triglycerides) is common side effect of sirolimus which can require treatment. The combination of cyclosporine and sirolimus is more nephrotoxic than cyclosporine alone. Other untoward problems are headache, nausea & diarrhea, leukopenia, and thrombocytopenia, Impaired wound, Healing Has been noted with Sirmus in obese patients and those with diabetes.

Drug interaction:
Avoid concomitant use of sirolimus with strong inducers (e.g., rifampin, rifabutin) and strong inhibitors (e.g., ketoconazole, voriconazole, itraconazole, erythromycin, telithromycin, clarithromycin) of CYP3A4 and Pgp.Grapefruit and grapefruit juice may interact with sirolimus and could lead to potentially dangerous effects Avoid eating grapefruit or drinking grapefruit juice while you are taking sirolimus. Cyclosporine and sirolimus should be administered at different timebecause both of these show interaction with each other.

Other immunosuppressive drugs and some possible futuredrugs:
1. Methotrexate
2. Glucocorticoids
3. Leflunomide
4. Antibodies
5. Rafamycin
6. Mizoribine
7. Brequinar sodium
8. Monoclonal antibodies .[1]

CONCLUSION

Immunosuppressive drugs are key therapeutic tools in the management of many rheumatic diseases Still, the side effects of these drugs can be severe, resulting in a shorter life expectancy for Transplant patients compared to the general population.[75]
The outcome of organ transplantation has majorly improved since the development of immunosuppressive drugs Thus, the development of new therapies that can induce immune tolerance in combination with No or limited side effects is needed.[76]
Fortunately, several novel strategies of immune tolerance induction are getting explored.

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