Advers Side effects Of Anti Proliferative Agents After Kidney Transplantation

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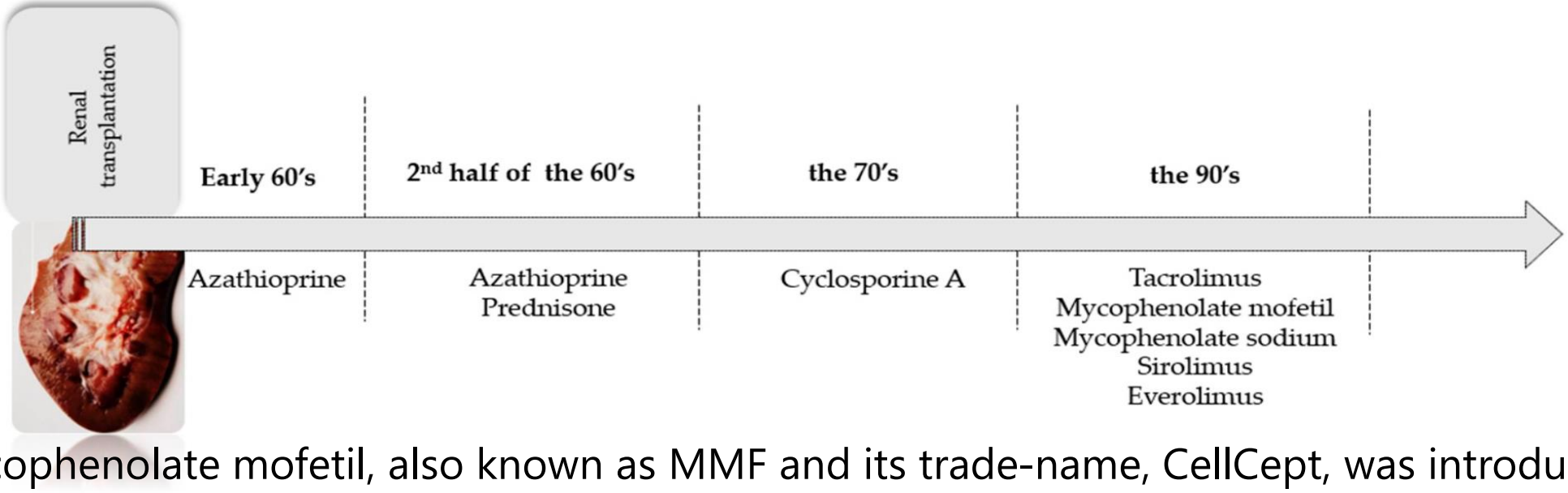
Februrary 2024

History

- Renal transplantation is now the best treatment for end-stage renal failure. Maintenance immunosuppression in kidney transplantation, for the majority of patients, relies on tacrolimus as the primary agent in combination with mycophenolate, with or without corticosteroids



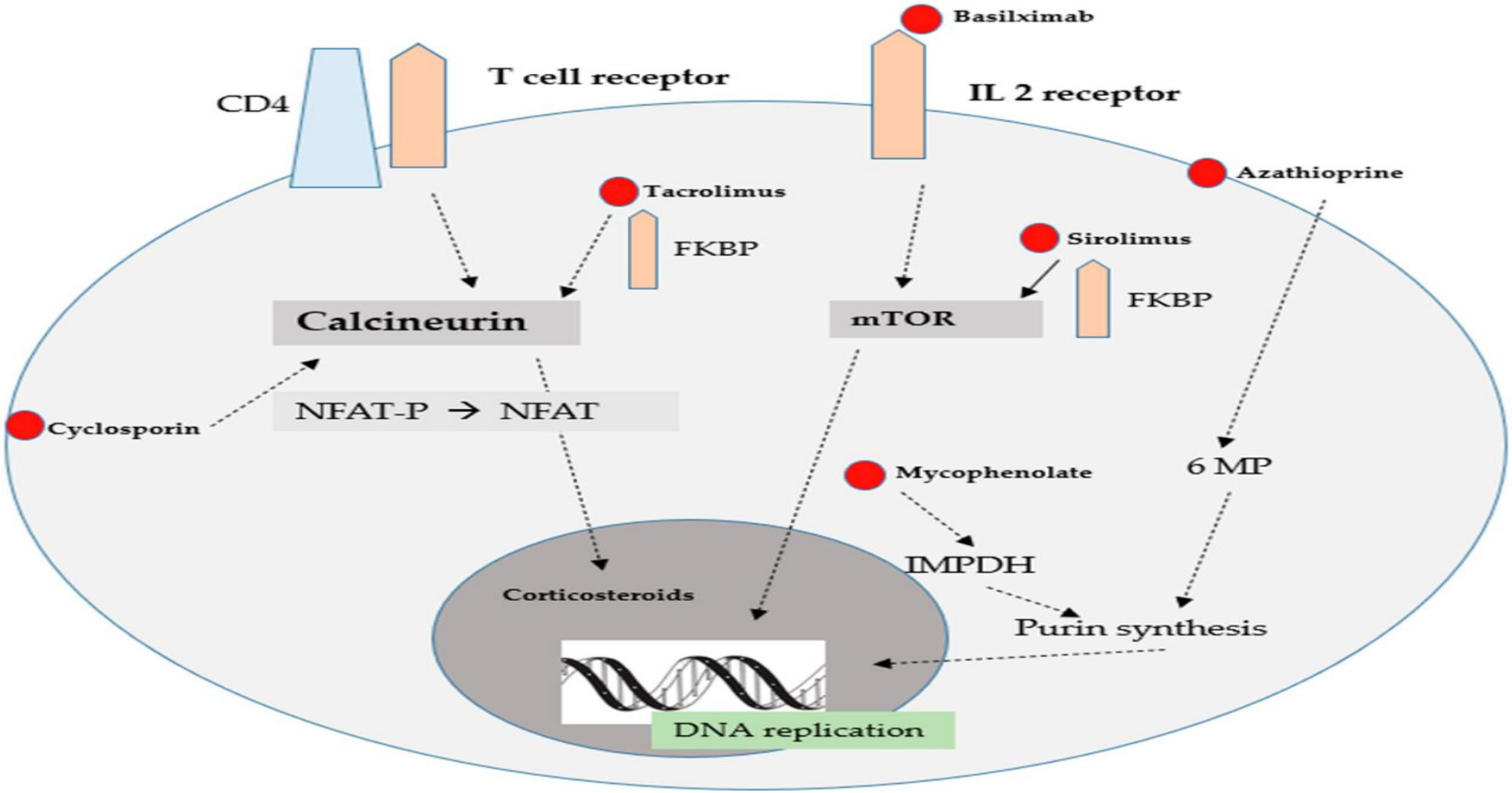
Mycophenolate mofetil, also known as MMF and its trade-name, CellCept, was introduced into clinical transplantation in 1995 and showed that it was more effective than azathioprine for the prevention of acute rejection in recipients of deceased donor kidney transplants when used in combination with cyclosporine and prednisone.

KDIGO Guide Line

- **KDIGO suggests using a combination of immunosuppressive medications as maintenance therapy including a CNI and an antiproliferative agent, with or without corticosteroids. (1B)**

- **KDIGO suggests that mycophenolate be the first-line antiproliferative agent. (2B)**

Anti Proliferative Drugs:

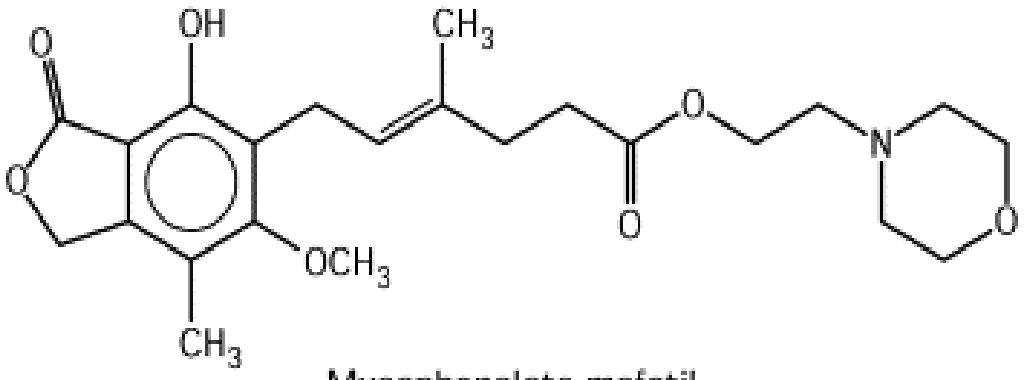


The mode of action of immunosuppressive drugs

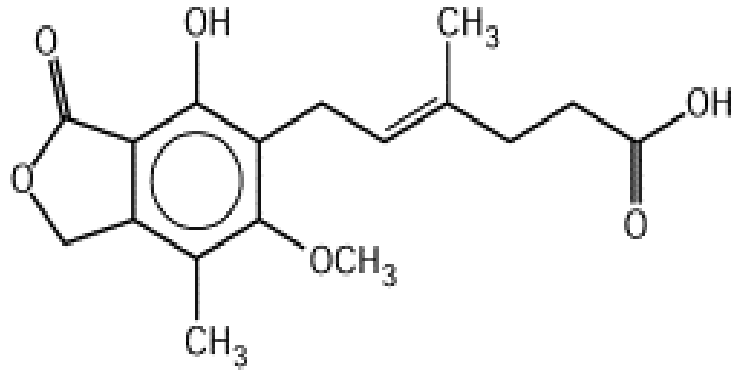
mycophenolic acid (MPA)

- Mycophenolate is a prodrug that was first isolated from the organism Penicillium brevicompactum.
- Mycophenolic acid (MPA) and its two clinically used derivatives, mycophenolate sodium and mycophenolate mofetil, are among the most widely used immunosuppressive drugs.

- MPA is the active metabolite of MMF and the molecule generally used for monitoring of MMF.



Mycophenolate mofetil



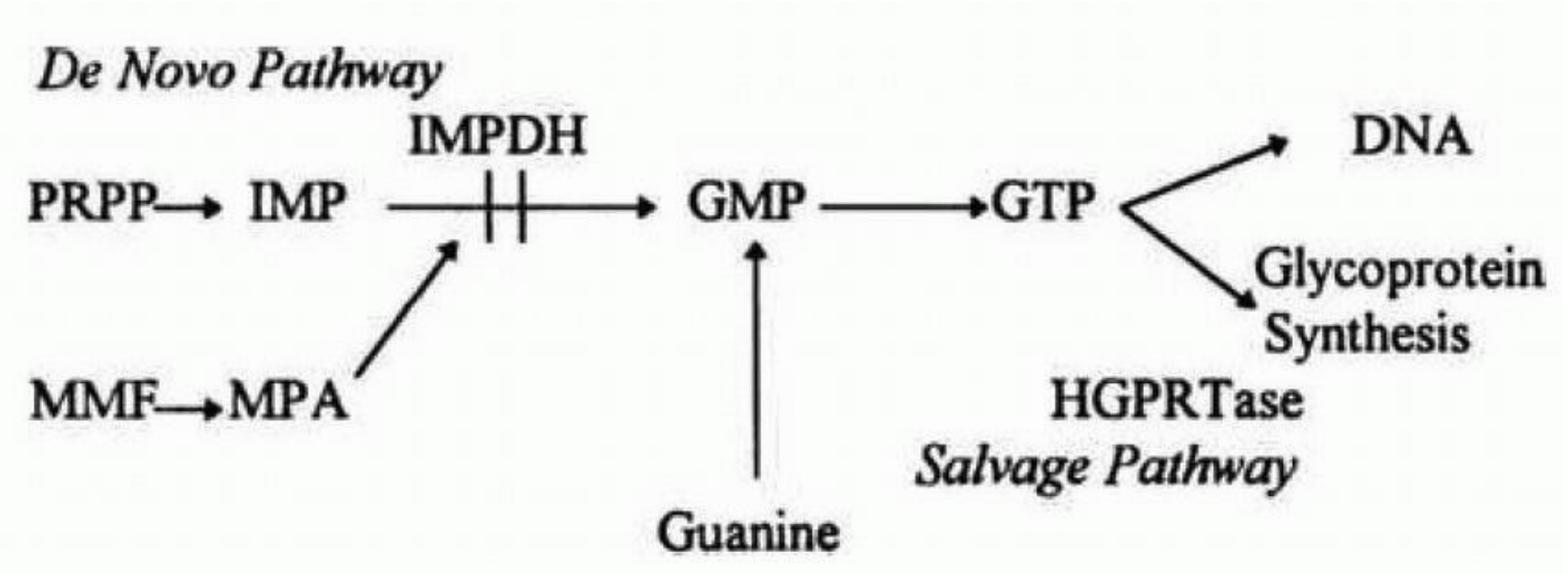
Mycophenolic acid

Pharmacodynamic

- It inhibits lymphocyte proliferation in preventing the rejection of the transplanted kidney . MPA is a reversible and incompetent inhibitor of the enzyme inosinomonophosphate dehydrogenase (IMPDH).

- Inhibition of the enzyme's activity results in impaired de novo guanine synthesis and DNA replication. This blocks the proliferation of T and B lymphocytes, which are dependent on the de novo purine synthesis pathway.
- Also, it inhibits antibody formation, and inhibits the generation of cytotoxic T cells but, it does not affect cytokine production or the more proximal events following antigen recognition.

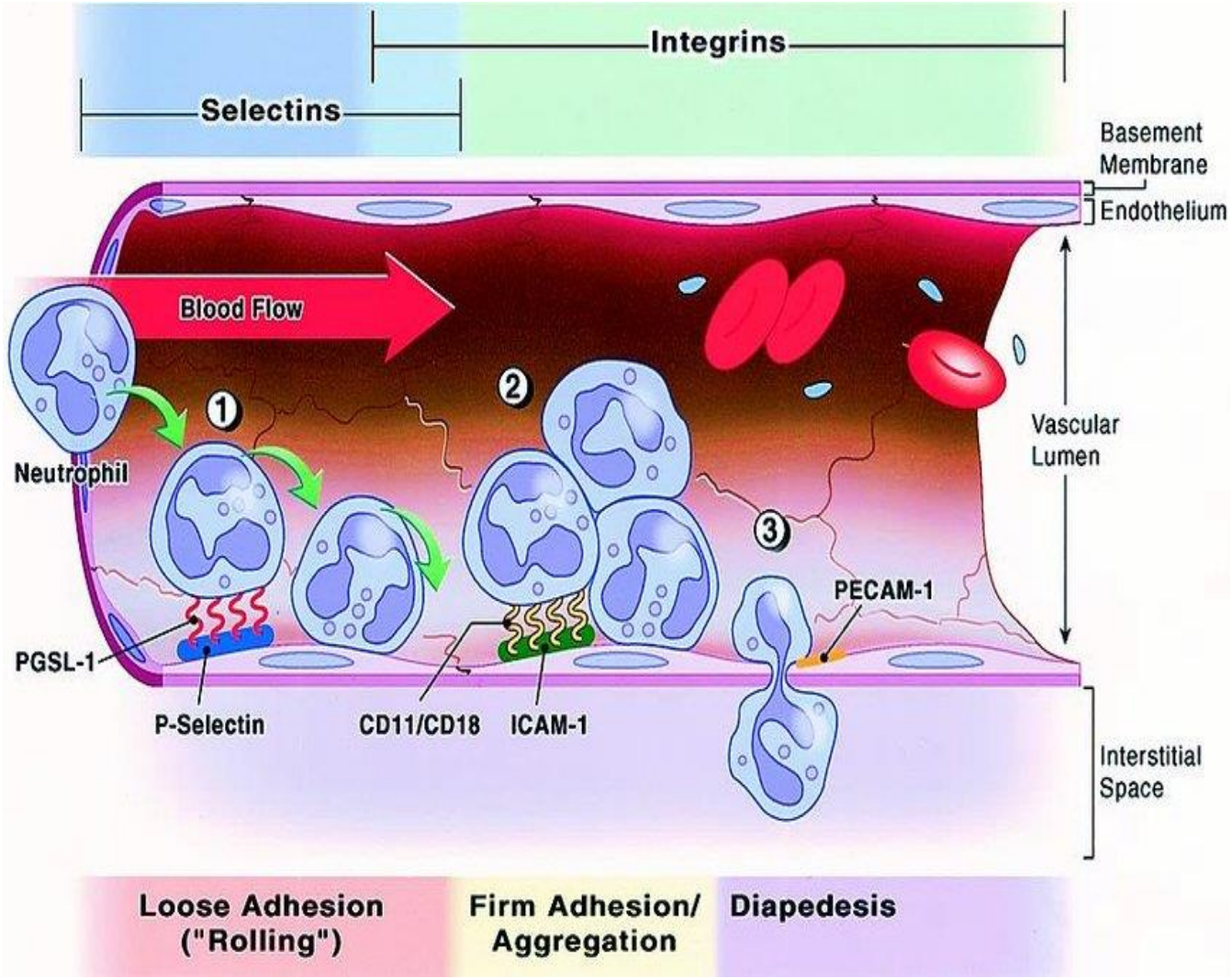
- Lymphocytes appear to rely on de novo purine synthesis more than other cell types that have a "salvage" pathway for production of guanosine nucleotides from guanine.



- MPAs also inhibit glycoprotein production by lymphocytes and monocytes, reducing their adhesion to endothelial cells .

- The capacity of MMF to treat ongoing rejection may be a reflection of its ability to inhibit the recruitment of mononuclear cells into rejection sites and the subsequent interaction of these cells with target cells.

- MMF may also exert a preventive effect on the development and progression of proliferative arteriolopathy, a critical pathologic lesion in chronic rejection ..



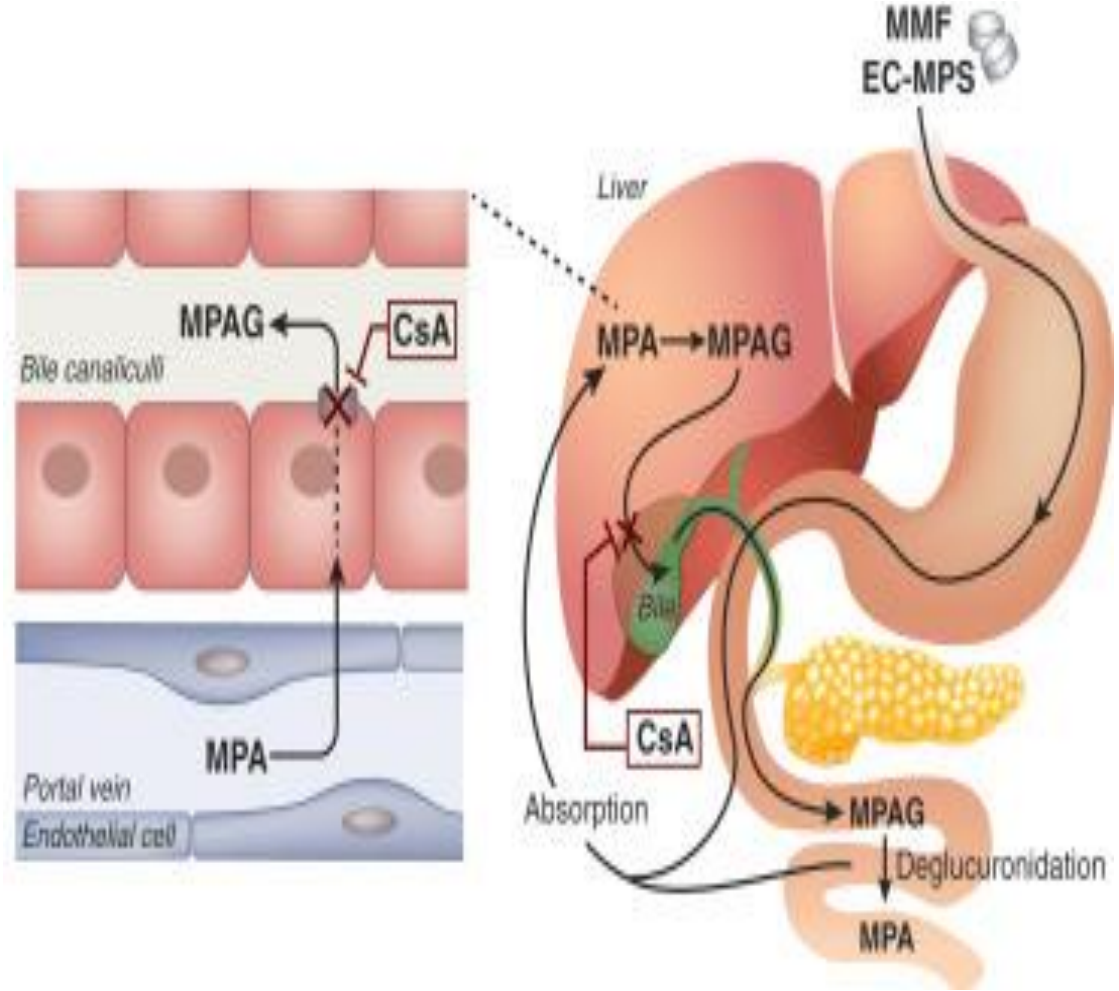
Pharmacokinetics

- The standard dose is 1 g twice daily. An intravenous preparation is available but is usually not required in kidney transplant recepient.
- CellCept is the morpholinoethyl ester of MPA and is available for clinical use in immediate release 250-mg capsules and 500-mg tablets.

- Myfortic (ecMPA) is a delayed-release formulation of MPA as a sodium salt and is available in 180-mg and 360-mg tablets: the standard dose when used is 720 mg twice daily.
- Orally administered MMF is hydrolyzed to MPA presystemically and is rapidly absorbed, producing a peak level in approximately 1 hour.
- The tablets only dissolve under neutral pH conditions, and thus absorption only occurs in the intestine. It has a peak concentration after approximately 2 to 3 hours.

How Cyclosporine lowers MPA concentrations

MMF is absorbed from the gut. The active metabolite, MPA, is glucuronidated in the liver, and excreted in bile as mycophenolic acid glucuronide (MPAG). In the gut, MPAG is deglucuronidated by bowel flora and MPA is reabsorbed, reflecting the enterohepatic recirculation. The biliary excretion of MPAG from the hepatocyte into bile is an active process, and the involved transporter protein is inhibited by cyclosporine(CsA). As a result, the recirculation is interrupted and exposure of MPA in plasma is reduced.



MMF monitoring

- **KDIGO suggests monitoring MMF levels. (2D)**

- The AUC is widely regarded as the best measure of overall drug exposure of MPA. Pharmacokinetic studies have demonstrated poor correlation of C0 with the full AUC.
- Mycophenolate mofetil has conventionally been adminis tered at a fixed dose without routinely monitoring MPA blood levels. Therapeutic drug monitoring during MMF therapy remains controversial.

- metabolization of MPAG to MPA by gut bacteria produces a second absorption peak of MPA that occurs at 6 to 12 hours following administration and may account for some of its GI side effects. This property also makes therapeutic drug monitoring of MPA difficult owing to the affect this secondary peak has upon the AUC.

- MPA has a half-life of 6 to 18 hours.
- The primary route of excretion is via the kidneys.
- The AUC of MPA is increased by renal impairment, although dose adjustments are not usually made.
- Neither MMF nor MPA is dialyzed.

Side Effects:

- Both MMF (CellCept) and enteric-coated MPA (Myfortic) are generally well tolerated and user friendly compounds.

❖GI tract:

- The **most common** adverse events are related to the GI tract, with diarrhea occurring in up to one-third of patients, and varying degrees of nausea, bloating, dyspepsia, and vomiting occurring in up to 20% of patients.
- Esophagitis and gastritis with occasional GI hemorrhage occur in about 5% of patients and may be associated with cytomegalovirus (CMV) infection.
- The incidence of GI side effects may be higher if the dosage is greater than 1 g twice daily. Most of these symptoms respond promptly to transient reduction of drug dosage. The total daily dose can also be split into three or four doses.

- The GI side-affect profile of the enteric-coated formulation of MPA **is not** statistically significantly different from the original formulation, though practitioners frequently switch formulations when GI side effects develop.
- Persistent administration of MMF or MPA in the face of diarrhea is strongly discouraged and can lead to an inflammatory colitis.
- As with the CNIs, food decreases its absorption; however, co administration with food may decrease the GI side effects.

- It is important to rule out treatable, underlying causes other than the immuno suppressive medication. Only after ruling out other underlying causes should reducing the MMF, or changing MMF to azathioprine, be considered.

Mycophenolate Induced Colitis: One-year Post-kidney Transplantation

Waleed Al Saadi[1], Issa Al Salmi[1,2]*, Ehab Mohammed[2], Zakiya Al Ajmi[3] and Suad Hannawi[4]

- This article reports a case of MMF-induced colitis in a young female patient that underwent a living-related kidney transplant. She presented with a three-month history of watery non-bloody and afebrile diarrhea. Investigations confirmed the diagnosis of MMF-induced colitis.

- MMF-induced enterocolitis is uncommon, and it may be associated with debilitating complications.This case shows a unique presentation of MMF-induced colitis with normal biochemical and imaging findings initially. Histopathological examination of colonic biopsies obtained during the colonoscopy procedure showed mildly increased crypt apoptosis, mild architectural disarray, and focal crypt attenuation; features consistent with MMF-induced colitis.

❖ *Bone Marrow Suppression:*

- Despite the relatively specific action of MPA on lymphocytes, leukopenia, anemia, and thrombocytopenia occur with a frequency similar to that seen with azathioprine and may require dose adjustment

Leukopenia

- Leukopenia is most likely to occur within **the first months** post-transplantation, whereas anemia might occur at any time post-transplantation, particularly when kidney allograft function is poor.

- transplant physicians use neutropenia to classify granulocytopenia based on its severity, utilizing the absolute neutrophil count (ANC) for its assessment.
- ANC < 1500/microliter is defined as neutropenia categorized as mild, moderate, or severe.

- Mild neutropenia has an ANC in the range of 1000 to 1500/microliter Moderate neutropenia is defined as 500 to 999/microliter. Severe neutropenia refers to ANC < 500/microliter.

- Neutrophils and lymphocytes play vital roles against infections, and leukopenic kidney-transplant recipients are prone to **opportunistic infections.** An ANC of less than 1000 cells per L increases susceptibility to infections. The frequency and severity of infections are increased with decreasing neutrophil **counts** and **prolonged** duration of neutropenia. *Escherichia coli* infections are more common in neutropenic kidney-transplant recipients

- Leukopenia is side effect of ATG, mycophenolate mofetil (MMF) or mycophenolic acid (MPA), valganciclovir as anti-cytomegalovirus prophylaxis and sulfamethoxazole-trimethoprim as anti-Pneumocystis jirovecii prophylaxis. Mycophenolate contributes to leukopenia, especially when it is associated with valganciclovir.

- When a mycophenolate-treated patient develops neutropenia, the area under the curve (AUC) can be ascertained to rule out overexposure.

- Management of severe leukopenia relies on **G-CSF** to achieve a quick recovery of WBC count when leukocytes are needed, in addition to **changes in immunosuppression** and **prophylaxis medications.**

❖ Anemia

- In 2003, a European survey (TRESAM study) showed A strong association between hemoglobin and graft function .
- Anemia was also more likely with therapy involving angiotensin- converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, mycophenolate mofetil, or azathioprine

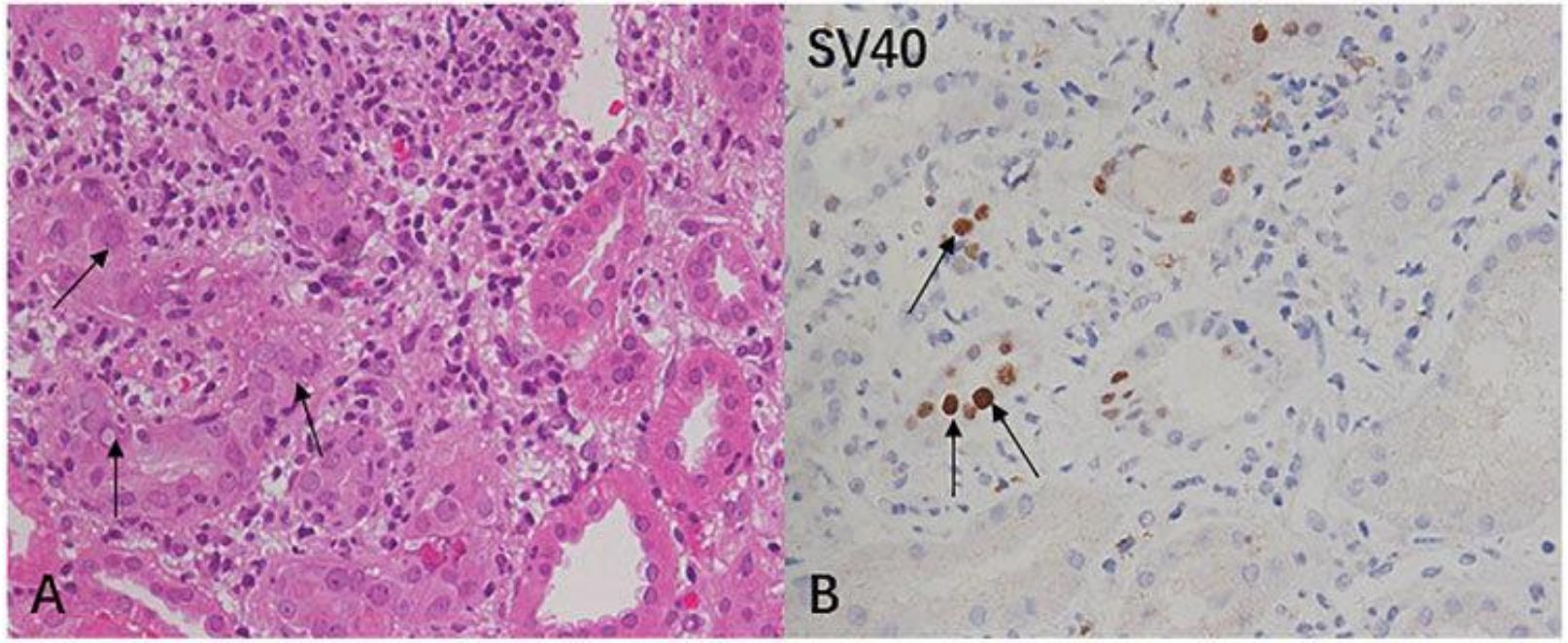
❖Thrombocytopenia:

Toxicity profiles of immunosuppressive medications

Adverse effect	Steroids	CsA	Tac	mTORi	MMF	AZA
New-onset diabetes mellitus	↑	↑	↑↑	↑		
Dyslipidemias	↑	↑		↑↑		
Hypertension	↑↑	↑↑	↑			
Osteopenia	↑↑	↑	(↑)			
Anemia and leucopenia				↑	↑	↑
Delayed wound healing				↑		
Diarrhea, nausea/vomiting			↑		↑↑	
Proteinuria				↑↑		
Decreased GFR		↑	↑			

❖ *Viral Reactivation*

- In most cases, viral reactivations occur **within the first months** after kidney transplantation. Induction and maintenance immunosuppression can lead to impaired immune responses, including antiviral responses, favoring opportunistic infections, such as cytomegalovirus (CMV) and BK virus (BKV) infections .These infections can impair graft function and contribute to transplant rejection.



BK virus:

Treatment of BKV nephropathy by modification of maintenance immunosuppression

Switching	Decreasing	Discontinuing
Tacrolimus→CsA (trough levels 100–150 ng/mL) (B-III)	Tacrolimus (trough levels < 6 ng/mL) (B-III)	Tacrolimus or MMF (maintain or switch to dual-drug therapy):
MMF→azathioprine (dosing ≤100 mg/day) (B-III)	MMF dosing ≤1 g/day (B-III)	CsA/prednisone (B-III)
Tacrolimus→sirolimus (trough levels <6 ng/mL) (C-III)	CsA (trough levels 100–150 ng/mL) (B-III)	Tacrolimus/prednisone (B-III)
MMF→sirolimus (trough levels <6 ng/mL) (C-III)		Sirolimus/prednisone (C-III)
MMF→leflunomide (C-III)		MMF/prednisone (C-III)

Progressive Multifocal Leukoencephalopathy

There are case reports of progressive multifocal leukoencephalopathy (PML) occurring in patients who have received treatment with MMF.

Neoplasia

- The incidence of lymphoproliferative disorders in all the various clinical trials of MMF is marginally greater than that seen in control.
- Patients who receive immunosuppressive agents are at increased risk of developing malignant neoplasms, including **lymphomas**. Among the patients who develop lymphoid malignancies, many are taking a combination of immunosuppressive agents, and therefore the risk attributable to a single agent is uncertain.
- For patients with a prior history of lymphoma, MMF should be avoided if other therapeutic options exist. For patients with a history of solid tumor malignancies, should be avoided if other therapeutic options exist.

Pregnancy

- MMF is a prodrug that is metabolized into mycophenolic acid, is contraindicated during pregnancy due to the reported fetal malformations, structural defects ,miscarriages, and deaths in human and animal studies. However, a recent study has reported successful administration of MMF in pregnancy; yet, since there is a lack of reliable information, MMF is not recommended.

- **KDIGO recommends that MMF and EC-MPS be discontinued or replaced with aza thioprine before pregnancy is attempted. (1A)**

- A characteristic phenotype associated with in utero exposure to MMF is emerging that includes cleft lip and palate, microtia, and absence of external auditory canals .

- European Best Practice Guide- lines suggest a 6-week window after discontinuing MMF and starting azathioprine, be fore pregnancy is attempted

Effects of Mycophenolate Mofetil in Isolation and in Combination with Testosterone on Sperm, Sex Hormones, and Antioxidant Enzymes in Male Rats

Fatemeh Hayati[1], *Homeira Rashidi[2], Ebrahim Soofari[3], Ghodrat Aalah Mohammadi[4]

MMF exerts adverse effects on sperm count, gonadotropins, testosterone, and antioxidant pathway enzymes. Moreover, it was revealed that the use of testosterone cannot reduce the adverse effects of MMF. The adverse effects of MMF can be ascribed to a decrease in the level of antioxidants.

The Clinical Manifestation of Immunosuppressive Therapy as a Tool to Improve Immune Monitoring in Renal Transplant Recipients

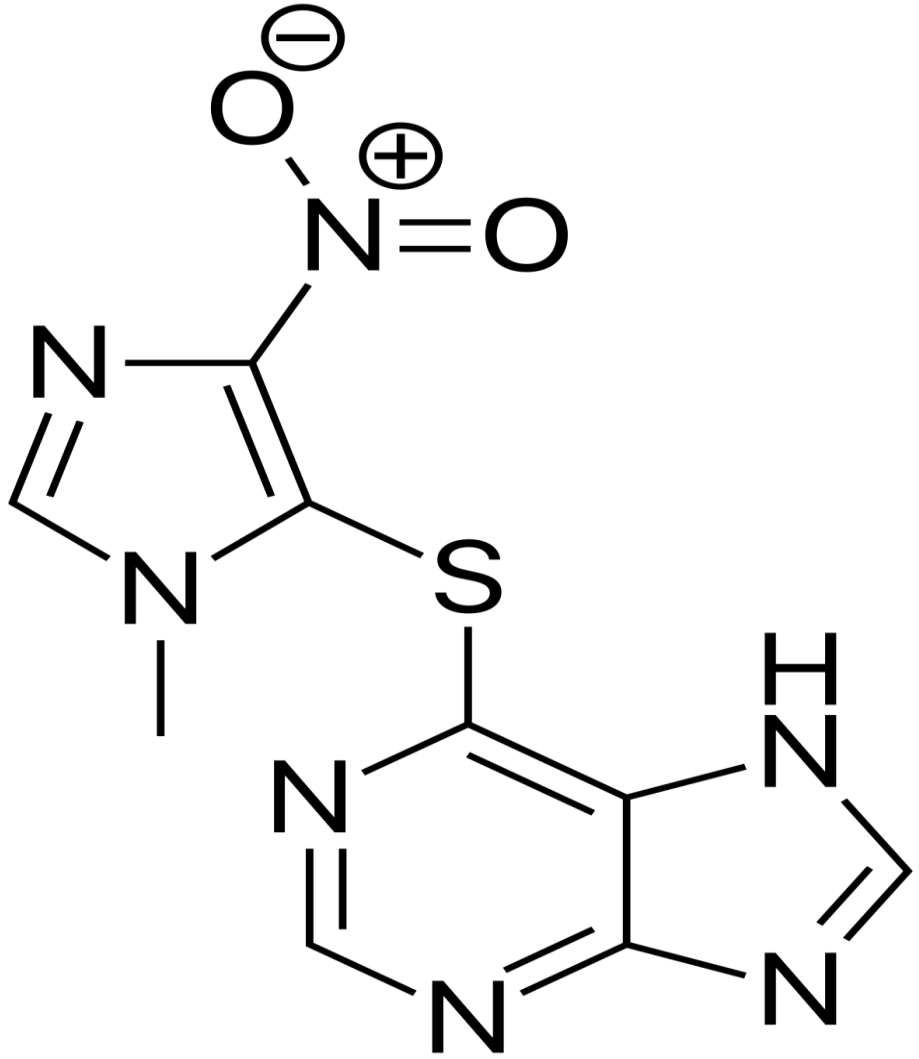
Noa Scott[a] Aharon Ben-David[a, b, c] Yana Davidov[a, d] Keren Cohen-Hagai[a, e]
Renana Yemini[f] Ronen Ghinea[a, b] Eytan Mor[a, b] Tammy Hod[a, b, c]

A questionnaire administered to RTRs was divided into physical (Q physical) and mental (Q mental) symptoms.
MPA-treated RTRs had higher mean scores for questions related to sleep disorders , to difficulty falling asleep , and to depression and anxiety.

RTRs should also be asked about feelings of fatigue, muscle weakness, night sweats, joint pain, and tremor. In patients who suffer from these symptoms, a reduction of overall immunosuppression should be considered.

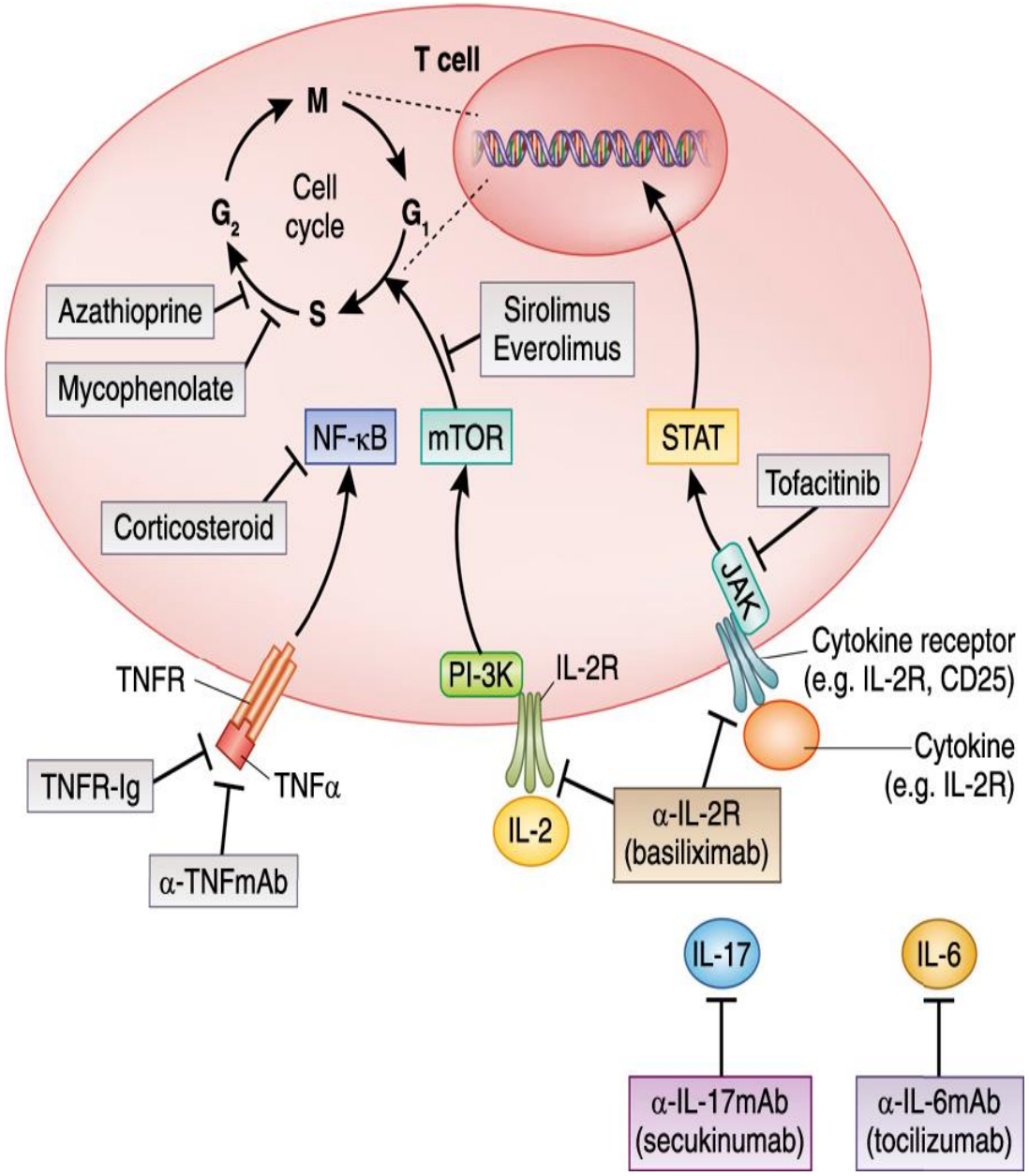
azathioprine

- azathioprine, was initially developed as an immunosuppressant in the 1960s, It is a purine analogue that mediates its effects by preventing the synthesis of nucleic acids.
- AZA is a pro-drug, and after oral ingestion and absorption, it is rapidly hydrolysed non-enzymatically to an imidazole derivative and 6-mercaptopurine (6-MP).
- 6-MP is also available for oral administration, AZA is usually preferred, as its bioavailability is more reliable.



Azathioprine is a purine analogue that is incorporated into cellular deoxyribonucleic acid (DNA), where it inhibits purine nucleotide synthesis and interferes with the synthesis and metabolism of ribonucleic acid (RNA).

Azathioprine inhibits the activation, differentiation, and proliferation of lymphocytes and reduces the activity of NK cells. These mechanisms produce an immunosuppressive effect, preventing the proliferation of cells involved in the initiation and enhancement of the immune response



- Azathioprine is a broad myelocyte suppressant. It inhibits the proliferation of promyelocytes in the bone marrow and, as a result, it decreases the number of circulatory monocytes capable of differentiating into macrophages. Thus, it is a powerful inhibitor of the primary immune response and is valuable in preventing the onset of acute rejection. It is ineffective in the therapy of rejection episodes.

Dose and Administration

- About half of orally administered azathioprine is absorbed; thus, the intravenous dose is equivalent to half the oral dose. Blood levels are not valuable clinically because its effectiveness is not blood level dependent.
- The drug is not significantly dialyzed or excreted by the kidney. Dose reduction is often practiced during kidney dysfunction, although it may not be necessary.
- When used as the primary immunosuppressant, the daily oral dose is 2 to 3 mg/kg. When used as adjunctive therapy with a CNI, the dose is 1 to 2 mg/kg.

Side Effects:

❖Hematologic: The most important side effects of azathioprine are hematologic.

- Complete blood counts, including a platelet count, should be performed **weekly during the first month of therapy**, and less frequently thereafter. Delayed hematologic suppression may occur.

❖Thrombocytopenia: It occurs in up to 5 percent of patients . Unless platelets are below 50,000/microL, which is uncommon, clinical bleeding or need for concurrent antiplatelet drug therapy **dose reduction is typically not required.**

Gastrointestinal

- Anorexia, nausea, and vomiting :They occur in up to 23 percent of patients treated with AZA; these symptoms usually begin **soon after** the initiation of therapy.
- hepatitis and cholestasis: It which usually present as reversible elevations in transaminase and bilirubin levels. The azathioprine dose is usually **reduced or stopped** during episodes of significant hepatic dysfunction.
- Pancreatitis: IT is a rare complication.

❖ Infection:

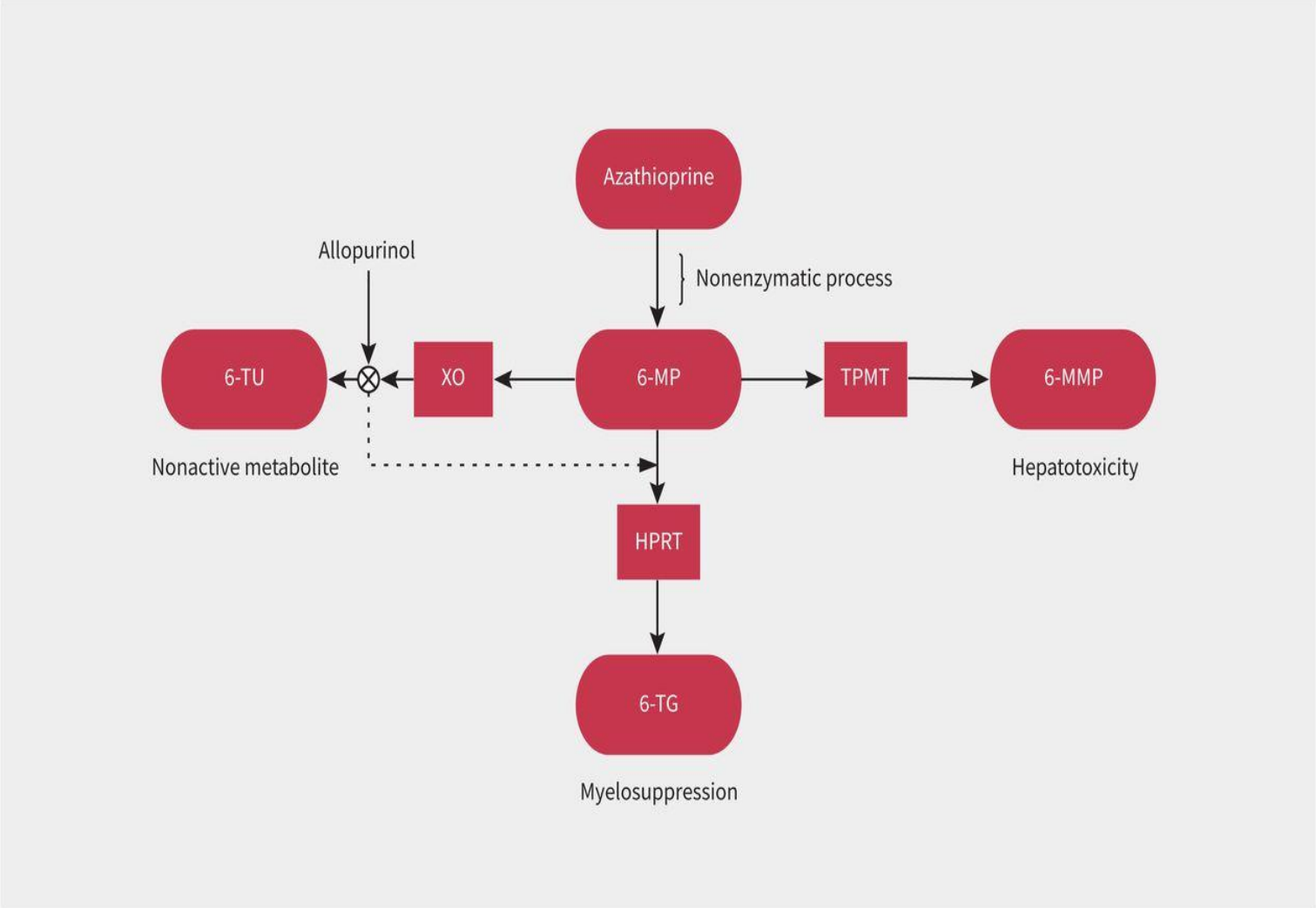
- Infections occur overall in up to 9 percent of patients. Bacterial infections usually occur in the clinical setting of leukopenia. Viral infections, especially **herpes zoster**, occur in up to 6 percent of treated patients. Exacerbation of chronic viral hepatitis may also occur.

❖Malignancy risk:

- There is some evidence suggesting a possible but small increased risk of malignancy in patients treated with AZA.

Hyperuricemia and azathioprine

- Allopurinol is a common uric acid lowering agent . Azathioprine is converted to inactive 6-thiouric acid by xanthine oxidase. The inhibition of this enzyme by allopurinol demands that this drug combination be avoided or used with great care.



- However, allopurinol and azathioprine used together can result in profound, life-threatening pancytopenia , and thus this combination should be used with extreme caution, or not at all. If used together, azathioprine should be reduced by at least 50% and frequent complete blood counts should be used to monitor the interaction . Further dose reductions may be needed.

- Mycophenolate does not interact with allopurinol and can be used in place of azathioprine if an antiproliferative agent is necessary for immunosuppression . Patients allergic to allopurinol may be given benziodarone

Pregnancy

- Azathioprine (AZA) is commonly prescribed for kidney recipients during pregnancy. Studies exploiting radioactive-labeled Azathioprine show that 64–93% of the azathioprine appears as inactive metabolites in fetal blood. In general practice, its dose is reduced during pregnancy since it carries the risk of low birth weight, small gestational age, and preterm birth.

- In adults, azathioprine is metabolized to 6MP (6 mercaptopurine); following inosinate pyrophosphorylase deficiency (due to the immature liver of fetus) required for the conversion of azathioprine to 6MP (active metabolite), the fetus is protected against the effects of drugs. Azathioprine doses > 6 mg/kg is teratogenic in animal studies.

- In human studies, LBW, prematurity, jaundice, respiratory distress syndrome (RDS), and aspiration have been observed. Azathioprine causes myelosuppression (suppressed bone marrow) in the fetus, and in cases where maternal leukocyte count < 7500/mm, infants are also at the risk of leukopenia.

- Interestingly, paternal (father) use of AZA is also characterized by congenital abnormalities. Preterm birth, abortions, cleft palate and lip and cardiac anomalies are also reported with the use of azathioprine.

Mycophenolate versus azathioprine

- Compared with placebo and azathioprine, mycophenolate reduces the risk of acute rejection; there is some evidence that mycophenolate improves long-term graft survival compared with azathioprine.

- Randomized controlled trials have shown that MMF (2 or 3 g, but not 1 g daily) is significantly better in preventing acute rejection than azathioprine.

- **In acute rejection KDIGO suggests adding mycophenolate if the patient is not receiving mycophenolate or azathioprine, or switching azathioprine to mycophenolate. (2D)**

MO983

EFFICACY AND SAFETY OF SWITCHING TO AZATHIOPRINE FOR MYCOPHENOLATE INDUCED DIARRHEA IN RENAL TRANSPLANT RECIPIENTS

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- A total of 177 patients, 59 of whom were switched to azathioprine due to diarrhea and 118 of which were matched control group without diarrhea that continued mycophenolate treatment, participated in this study

- Although switching mycophenolate to azathioprine was an effective approach to improve diarrhea, this approach is associated with increased risk of graft loss.

Thanks