بسم الله الرحمن الرحیم

Mycophenolic acid side effects

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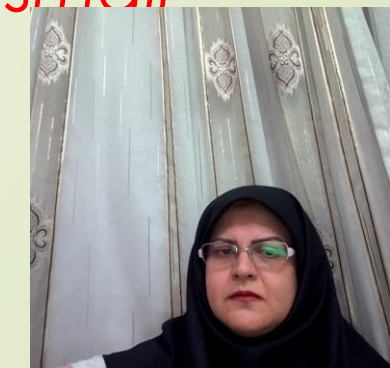
Introduction

- MPA is an inhibitor of inosine monophosphate dehyrogenase, which is required for de novo pathway synthesis of guanosine from inosine
- The effects of MPA is relatively lymphocyte specific as, lacking a purine salvage pathway, T and B cells rely exclusively on de novo purine synthesis
- By limiting the proof of available guanosine triphosphate, MPA prevents T and B lymphocyts replication and suppresses both the cellular and humoral immune responses

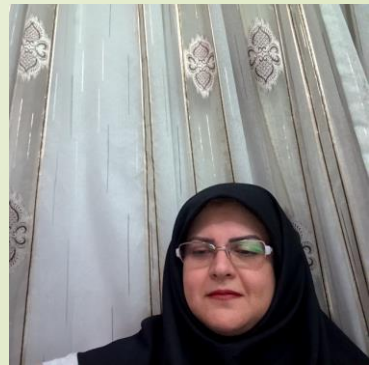
Introduction

- Mycophenolate (also known as mycophenolic acid [MPA]) is available in two different formulations: mycophenolate mofetil (MMF) and enteric-coated mycophenolate sodium (EC-MPS)
- *These formulations have different absorption characteristics.*
- *EC-MPS has the potential to reduce the incidence of adverse gastrointestinal (GI) effects, principally diarrhea, by delaying release of MPA into the small intestine instead of the stomach.*



Side effects

Gastrointestinal (GI) symptoms and dose-related bone marrow suppression are the most commonly observed adverse effects, but these usually resolve with dose adjustments

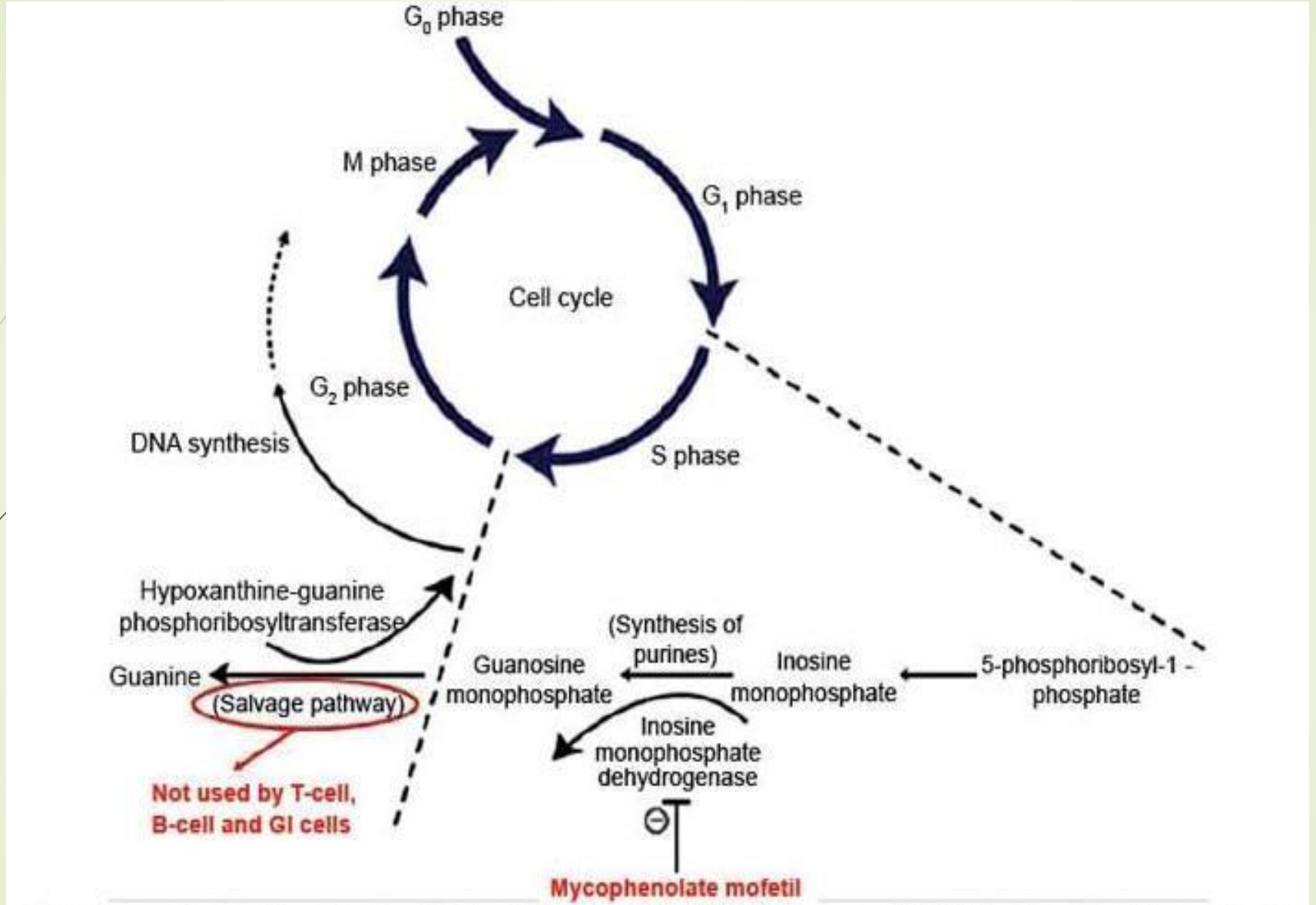


Gastrointestinal side effects

- Persistent diarrhea, the most frequent adverse reaction to mycophenolate, is the principal reason underlying its discontinuation. Dose reduction and/or withdrawal of MMF due to gastrointestinal complications has been associated with an increased risk for rejection and allograft failure.
- *Mycophenolate sodium (EC-MPS), an enteric-coated formulation of mycophenolate, was developed to try to improve the upper gastrointestinal tolerability of mycophenolate*.
- EC-MPS and MMF are similar in both efficacy and safety

Gastrointestinal side effects(histopathologic changes)

- The histopathologic changes associated with GI symptoms have been studied in a retrospective series of solid organ transplant recipients who had undergone diagnostic colonic biopsies for such symptoms.
- Abnormal findings were observed in 69 percent of 32 patients with GI symptoms on MMF (500 to 1000 mg twice daily), including changes suggestive of inflammatory bowel disease (28 percent), graft-versus-host disease (19 percent), ischemia (3 percent), or self-limited colitis (16 percent)
- By comparison, only one of eight patients not on MMF had significant changes, a mild graft-versus-host disease-like patt



: Diagram showing the mechanism of action of Mycophenolate. IMPDH is the enzyme inhibited by Mycophenolate, arresting the cell cycle in the S phase. All cells of the body except lymphocytes and GI cells use the salvage pathway with help of the enzyme HGPRT to complete the cell cycle.

Mechanism of MPA induced diarrhea

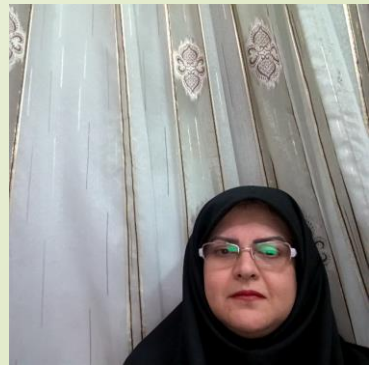
- MPA inhibits the enzyme IMPDH, which decrease de novo purine synthesis affecting GI epithelial cell replication(*since most GI cells do not use the salvage pathway for replication*). This leads to villous atrophy, malabsorption, and diarrhea.
- MPA gets metabolized to acyl glucuronidase, which in turn trigger the immune system leading to hypersensitivity, inflammation, and autoimmune reactions in the gut, presenting as enterocolitis simulating an inflammatory bowel disease.

Gastrointestinal side effects

- Nausea, vomiting, diarrhea, abdominal cramps, constipation, soft stools, and frequent stools.
- Rare GI side effects have been identified and include gastrointestinal hemorrhage, oral ulceration, esophagitis, gastritis, doudenitis, villous atrophy, and ischemic colitis.
- MPA side effects are dose dependent and occurs in up to 20% of patients at doses of 2 gr daily orally.

Gastrointestinal side effects

Starting with lower doses at first (eg, 500 mg daily for several days) may improve a patient's GI tolerance of MMF. After several days, the dose of MMF may typically be increased to the target dose over a few weeks.

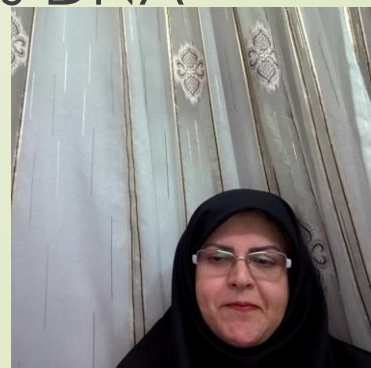


Bone marrow suppression

- Cytopenias are major potential concerns and require regular monitoring. Complete blood counts (CBCs) should be performed after the first one to two weeks of therapy and then once every six to eight weeks thereafter if no cytopenia is noted
- Hematologic side effects, such as leukopenia, anemia, and thrombocytopenia, are relatively uncommon, observed in fewer than 5% of patients treated with MPA
- *These side effects are usually mild, dose related, and reversible with discontinuation of therapy or dose reduc*

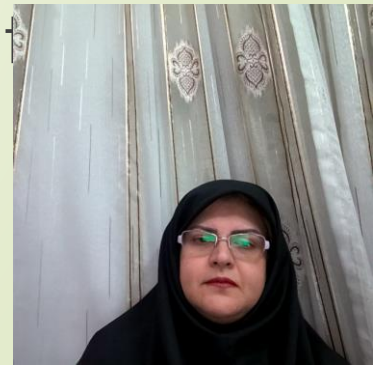
Mechanism of MPA

- MPA inhibit T lymphocyte proliferation by decreasing de novo guanosine production and ultimately DNA synthesis in T lymphocytes
- MPA, increase apoptosis in human T lymphocytes, specially in activated T lymphocytes
- MPA exhibited a dose dependent decrease in cytotoxic T cell activity in mice
- MPA inhibits B cells via inhibition of IMPDH, and thus DNA synthesis in B lymphocytes, and also MPA inhibits immunoglobulin production occurred



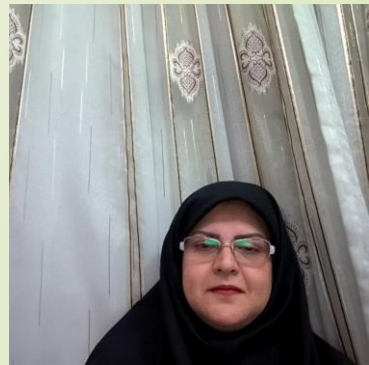
Mechanism of MPA

- MPA, in vivo, inhibit the capacity of dendritic cells to efficiently present antigens to T lymphocytes
- MPA reduces the recruitment of monocytes into sites of graft rejection and inflammation, and also increases the apoptosis of monocytes
- MPA directly influences the function of endothelial cells, specifically disrupting leukocyte adhesion
- The recruitment of lymphocytes and monocytes int inflammatory tissues is decreased by MPA



Opportunistic infection

- In patients treated with MPA, especially when exceeding doses of 2 gr daily
- Organ transplant recipients, the majority of cases were noted in patients simultaneously treated with other immunosuppressive agents



Opportunistic infections

Reported infectious complications in organ transplant recipients include

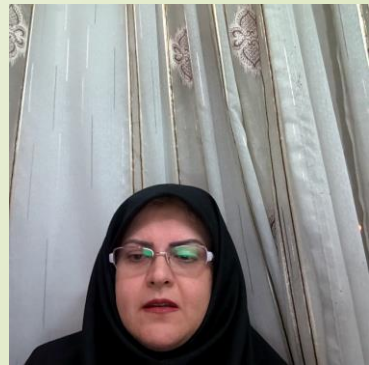
- Herpes simplex infection, herpes zoster, human herpes virus type 6, human papilloma virus infection, aspergillosis, cryptococcosis, candidiasis, mucormycosis, CMV infection, *P. jirovecii and pediatric disseminated varicella*

Pneumocystis jirovecii

- Although it is somewhat counterintuitive, there is some reason to believe that MMF exerts a protective effect against *P. jirovecii*.
- In animal models, MMF demonstrates an antimicrobial effect against this organism.
- Moreover, in four randomized, controlled trials of MMF in renal allograft transplant recipients, none of the 1068 patients who received MMF (compared with 10 of the 563 patients who did not) developed *P. jirovecii* infections

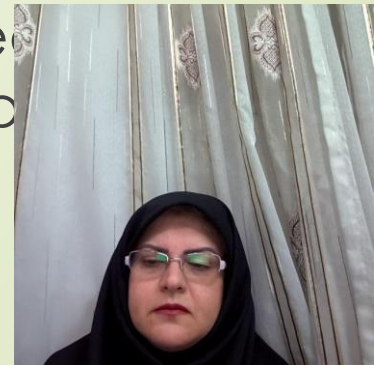
Pneumocystis jirovecii

- It has been well established that MMF has antimicrobial properties against *Pneumocystis jirovecii* (*P. jirovecii*) pneumonia. Therefore, the use of PCP prophylaxis among patients who are receiving treatment with MMF is somewhat controversial and is largely driven by the underlying disease.



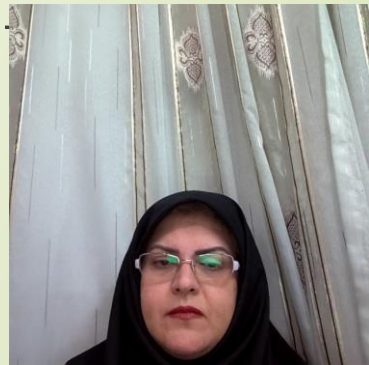
Viral infections

- In one study of heart transplant recipients, a higher incidence of herpes zoster was associated with MMF. Of greater concern, however, is the risk of cytomegalovirus (CMV) infection.
- A higher incidence of tissue-invasive CMV infections has been documented in clinical trials of renal allograft recipients who received MMF as part of their immunosuppression regimens
- This same increase in incidence of tissue-invasive CMV infections has not been observed in trials of patients tre with MMF who have received liver, heart, or lung transp



Viral infections

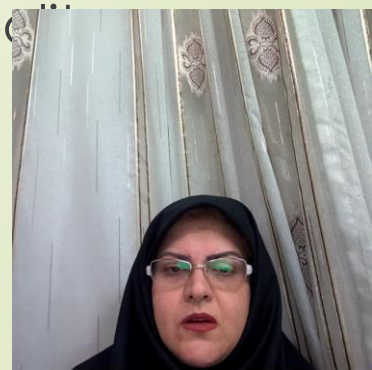
- The data regarding the impact of MMF on the reactivation of viral hepatitis are even murkier. There is evidence that, in vitro, MPA suppresses both the expression of hepatitis B surface antigen and HBV viral replication .
- An open-label cohort study indicated that treatment with MMF was associated with a lower risk of HBV reactivation than treatment with high-dose glucocorticoids alone , implying that MMF may exert a protective effect against HBV reactivation.
- Similarly, there are both in vitro and in vivo data indicat that MMF may inhibit HCV replication



Patients who develop an infection

- In patients with life-threatening infections or evidence of sepsis, we withhold all immunosuppressive agents, except for low-dose glucocorticoids. We usually restart the calcineurin inhibitor within one week from the time it was withheld but discontinue the antimetabolite indefinitely.
- In patients with moderate infection (ie, who require admission and intravenous antibiotics but are not septic), we withhold one agent (typically the antimetabolite, such as mycophenolate or azathioprine).

We usually hold this agent for four to six weeks and restart it at 50 percent of the dose that was administered prior to the infection. In patients with recurrent infection, we discontinue the antimetabo[illegible] indefinitely.

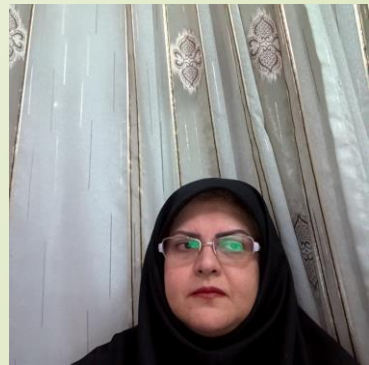


Progressive multifocal leukoencephalopathy

There are case reports of progressive multifocal leukoencephalopathy (PML) occurring in patients who have received treatment with MMF. In a retrospective cohort study of over 32,000 renal transplant recipients in the United States, the incidence of PML was 14.4 cases per 100,000 person-years versus zero cases among the non-MMF users, but the difference was not statistically significant.

Neoplasia

- Patients who receive immunosuppressive agents are at increased risk of developing malignant neoplasms, including lymphomas.
- However, one reported case of central nervous system lymphoma that occurred during mycophenolate monotherapy for myasthenia gravis suggests that MMF use alone may confer an increased risk of lymphoid neoplasia .



Neoplasia

- MMF prescribing information includes a specific warning about lymphoma and other neoplasms as a result of immunosuppression.
- *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, the specific risks associated with comparable immunosuppressive regimens are less clear

Contraindiactions

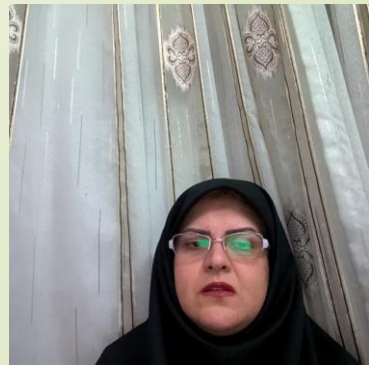
Pregnancy — Mycophenolate increases the risk of first-trimester pregnancy loss and congenital malformations, including cleft lip and palate, as well as anomalies of the distal limbs, heart, esophagus, and kidneys

Lactation — Mycophenolate is excreted into breast milk and is contraindicated in women who are breastfeeding

Active infection

Warning

- Do not use mycophenolate in female recipients of childbearing age unless they are on long-acting contraception, have undergone surgical sterilization procedures, or have absolute infertility.
- Mycophenolate is teratogenic, and its use is contraindicated in pregnancy. Thus, in these patients, we prefer to use azathioprine, which does not seem to have a detrimental effect on fertility or pregnancy



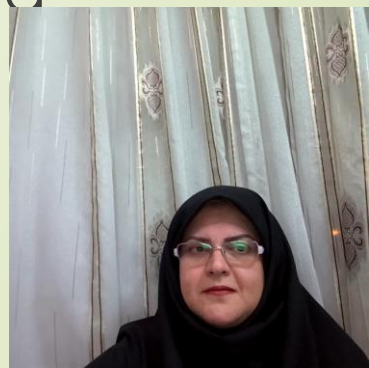
- Mycophenolic acid can make sunburn more easily. Avoidance of sunlight or tanning beds is very important. when the patient is outdoor, wearing protective clothing and use sunscreen (SPF 30 or higher) is necessary.

- The patient must not donate blood or sperm while using mycophenolic acid.

Side effects

Common adverse drug reaction_(≥ 1% of people) include diarrhea, nausea, vomiting, joint pain; infections, leukopenia , or anemia reflect the immunosuppressive and myelosuppressive nature of the drug.

Mycophenolate sodium is also commonly associated with fatigue, headache, cough and/or breathing issues. Intravenous (IV) administration of mycophenolate mofetil is also commonly associated with thrombophlebitis and thrombosis



Thank for attention