Inosine monophosphate inhibitors in transplantation

By Dr. M.Zaare

Assistant professor

Nephrologist

- Mycophenolate mofetil(MMF, CellCept) was introduced into clinical transplantation in 1995.
- MMF is a prodrug, active compound of which is mycophenolic acid (MPA)
- MPA has poor bioavailability, but this was solved by addition of the morpholinoethyl ester
- An enteric-coated form of MPA (ERL-080, Myfortic) became available in 2004.

Pharmacodynamics

Mechanism of Action.

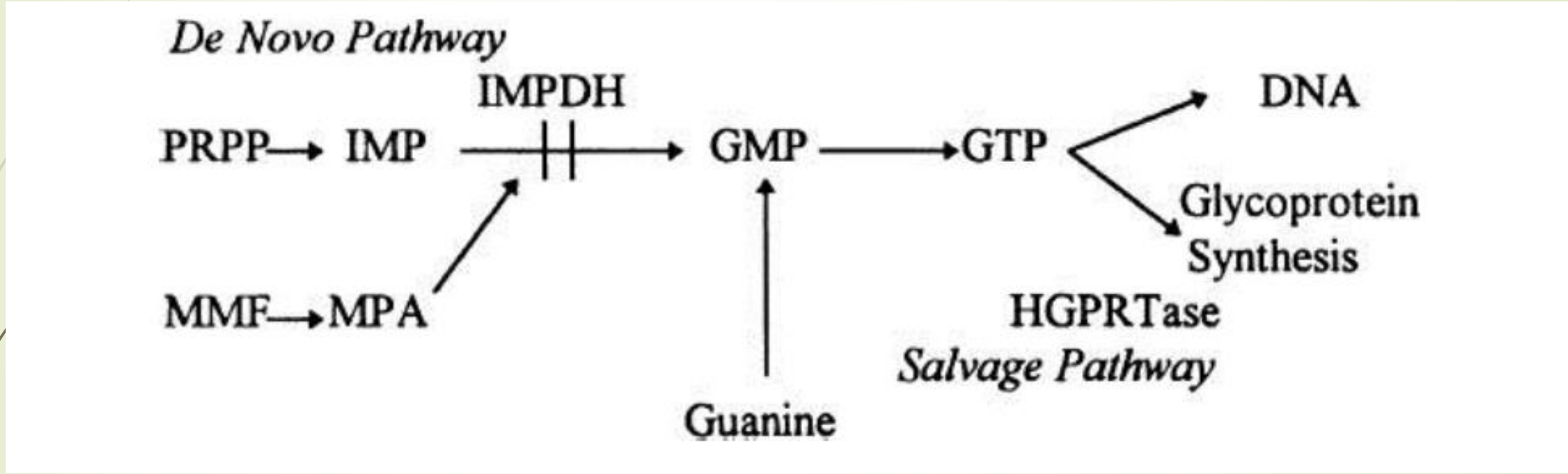
MPA: reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH).

IMPDH is a critical, rate-limiting enzyme in the synthesis of purines.

IMPDH catalyzes the formation of guanosine nucleotides from inosine.

Depletion of guanosine nucleotides by MPA has relatively selective antiproliferative effects on lymphocytes.

- MFA is potent inhibitor of the type II isoform of IMPDH. The type II isoform is more expressed in activated lymphocytes than the type I isoform of IMPDH, which is expressed in most other cell types
- 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


De Novo Pathway
IMPDH
PRPP
IMP
GMP
GTP
DNA
Glycoprotein
Synthesis
MMF
MPA
HGPRTase
Salvage Pathway
Guanine

MPA

- blocks the proliferation of T and B cells
- inhibits antibody formation
- inhibits the generation of cytotoxic T cells
- downregulates the expression of adhesion molecules on lymphocytes
- impairing lymphocytes binding to vascular endothelial cells
- inhibit the recruitment of mononuclear cells into rejection sites
- preventive effect on the development and progression proliferative arteriolopathy(critical pathologic lesion in chronic rejection)

- MMF reduces the rate of late allograft loss

Adverse Side Effects

- Both MMF (CellCept) and enteric-coated MPA (Myfortic) are generally well tolerated and user-friendly compounds.
- GI tract: diarrhea (up to one-third of patients), nausea, bloating, dyspepsia, and vomiting (up to 20% of patients) ,esophagitis and gastritis with occasional GI hemorrhage (5% of patients)
  - 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.
  - Persistent administration of MMF or MPA in the face of diarrhea is strongly discouraged and can lead to an inflammatory colitis.
  - coadministration with food may decrease the GI side effects.

- leukopenia, anemia, and thrombocytopenia: require dose adjustment
- Leukocytosis
- lymphoproliferative disorders and opportunistic infections
- progressive multifocal leukoencephalopathy (PML): rare
- Congenital malformations:
  - ear malformations
  - spontaneous abortions

azathioprine is often used to replace the MMF. No dose adjustment is required in males anticipating fatherhood.

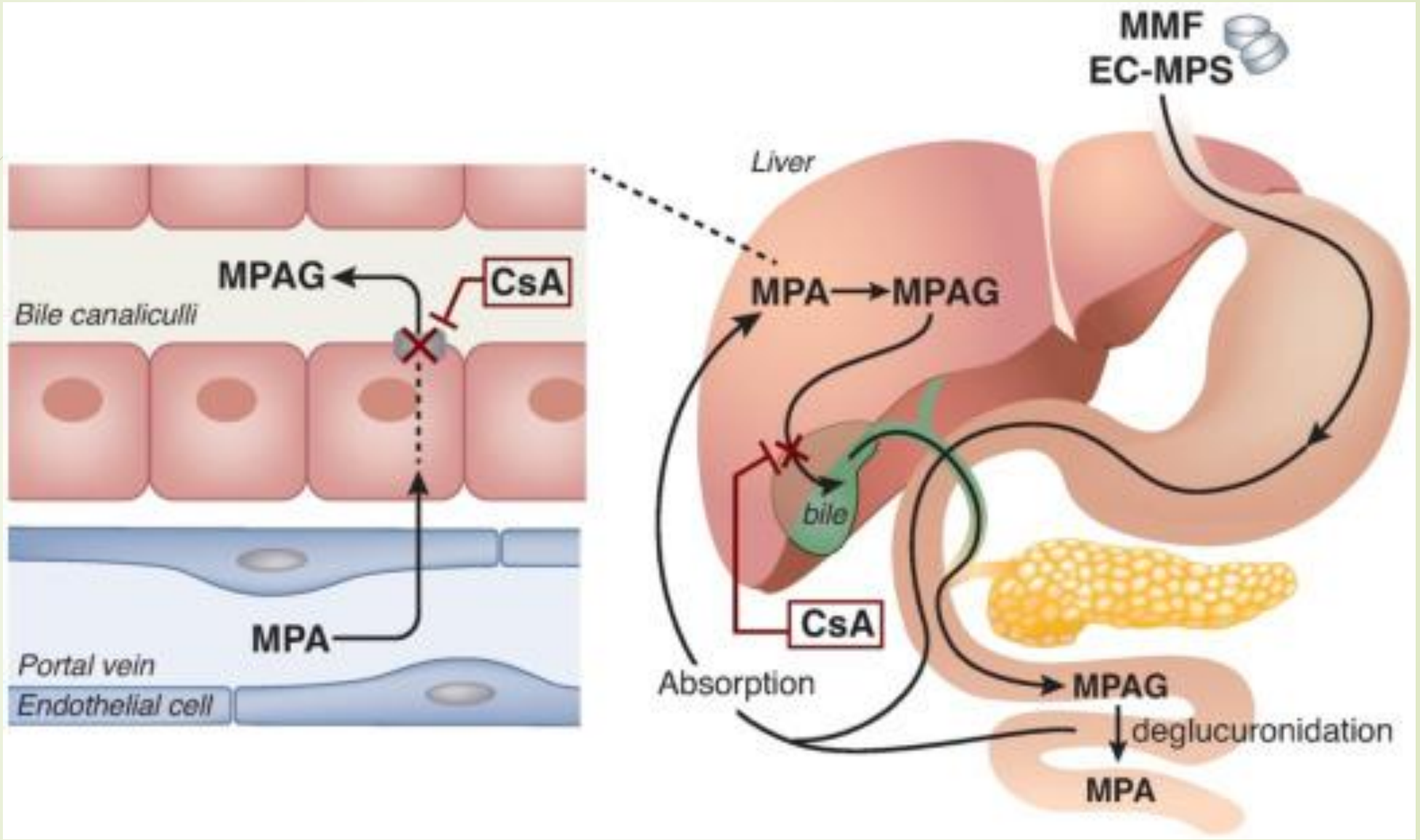
Pharmacokinetics

- **Formulations.**
  - CellCept:
    - immediate release
    - morpholinoethyl ester of MPA (250-mg capsules ,500-mg tablets, suspension formulation)
    - standard dose is 1 g twice daily
  - Myfortic (ecMPA):
    - delayed-release
    - sodium salt (180-mg and 360-mg tablets)
    - standard dose when used is 720 mg twice daily

- *Absorption and Distribution*
  - MMF (Oral) → hydrolyze → MPA → absorbed (peak level in 1 hour)
  - bioavailability of MMF: 90%
  - MPA protein bound to albumin: 97%
  - tablets only dissolve under neutral pH conditions → absorption only occurs in the intestine (peak concentration after approximately 2 to 3 hours)
  - the AUC of MPA increases with time; the same doses when used early postoperatively can produce much higher concentrations several months later

- *Metabolism and Excretion*
  - MPA → MPAG (pharmacologically inactive form)

    glucuronyl transferase enzymes
  - Enterohepatic cycle transport MPAG from the liver into the bile → Gut bacteria → metabolize the MPAG to MPA(second absorption peak at 6 to 12 hours following administration)
    - An external bile drain (not unusual after liver transplantation) or broad spectrum antibiotics (eliminating the glucuronidase activity on the gut flora) can also interrupt the enterohepatic recirculation and lead to a drop in MPA concentrations
    - Enterohepatic cycling of MPAG can occur via OATP transportation of MPAG from the liver into the bile. Cyclosporine lowers MPA concentrations by decreasing its enterohepatic recycling via OATP1B1 inhibition.


MMF
EC-MPS
Liver
MPAG
CsA
Bile canaliculli
MPA → MPAG
bile
MPA
Portal vein
Endothelial cell
CsA
Absorption
MPAG
deglucuronidation
MPA

- MPA has a half-life of 6 to 18 hours
- route of excretion: kidneys (as MPAG, with minimal amounts of MPA excreted unchanged)
- renal impairment: AUC of MPA is increased, dose adjustments are not usually made
- Neither MMF nor MPA is dialyzed

- *Pharmacokinetic and Pharmacodynamic Drug–Drug Interactions*
  - MMF and azathioprine: should not be administered concomitantly (hematologic toxicity)
  - MMF and sirolimus: Standard hematologic parameters must be carefully followed
  - MMF and Cyclosporine : decreasing MMF enterohepatic recycling. (it is not seen with everolimus, sirolimus, or tacrolimus→ maintenance dosage of MMF 500 to 750 mg twice daily)
  - MMF and {antacids, cholestyramine, sevelamer, or oral ferrous sulfate}: should not be administered simultaneously
  - MMF and allopurinol: its OK
  - MMF and acyclovir or ganciclovir: it is wise to discontinue MMF when there is necessitating use of high dosages of the antiviral drugs.

Conventional Immunosuppressive Protocol

- CNI + adjunctive agent + corticosteroids +/- antibody induction
- 90% to 95% graft survival with an acute rejection rate of 10% to 20%

Class of Agent	Options
Calcineurin inhibitor	Cyclosporine, tacrolimus
Corticosteroids	Dose and regimen
Adjunctive agent	Azathioprine, MMF, sirolimus
Antibody induction	Lymphocyte depleting or nondepleting
Supplementary agents	CCB, HCRI
Infection prophylaxis	Bactrim, antifungals, antivirals

CCB, calcium channel blocker; HCRI, HMG-CoA reductase inhibitor; MMF, mycophenolate mofetil.

Which Adjunctive Agent?

- Azathioprine: has been replaced by MMF or enteric-coated MPA
- MMF or enteric-coated MPA: superior capacity to reduce the incidence of acute rejection and evidence.
  - The MMF/MPA combination with tacrolimus is used in over 90% of patients in the United States.
- Sirolimus: drug-level monitoring of sirolimus is mandatory
  - Indication:
    - high risk for post-transplantation malignancy
    - *de novo* malignancy, especially skin cancer, after transplantation
- Everolimus: can be used as a primary immunosuppressant

Specific Protocol Recommendations

- The standard dose of MMF in adults is 1,000 mg twice daily, although African-American patients may benefit from a higher dose (1,500 mg twice daily) in the early post-transplantation period.
- Patients on full-dose tacrolimus may require a lower dose.
- If the dose of MMF is reduced or held for short periods in the event of side effects, the dose of CNI and prednisone should be maintained. The longer the MMF dose is reduced, the greater is the risk for subsequent rejection, and patients should be monitored accordingly.
- Most programs continue to administer MMF for prolonged periods.