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Review on Overview of Mycophenolate Mofetil

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Abstract: *Mycophenolate mofetil (MMF, CellCept®) serves as a prodrug for mycophenolic acid (MPA), an inhibitor of inosine monophosphate dehydrogenase (IMPDH), the key enzyme in guanosine nucleotide de novo synthesis. T- and B-lymphocytes rely more on this pathway than other cell types. Notably, MPA strongly inhibits the type II isoform of IMPDH in activated lymphocytes, making it more cytostatic for lymphocytes than other cells. This mechanism underlies MPA's potent immunosuppressive effects. CellCept® dampens T-lymphocytic responses to allogeneic cells and antigens. It inhibits primary antibody responses but not secondary ones. The effectiveness of regimens with CellCept® for preventing allograft rejection and treating rejection is well-established. CellCept® demonstrates efficacy in various experimental animal models of chronic rejection, raising hopes for similar effects in humans. Mycophenolate mofetil, an ester prodrug of the active immunosuppressant mycophenolic acid, acts as a noncompetitive, selective, and reversible inhibitor of inosine monophosphate dehydrogenase. This enzyme is crucial in the de novo synthesis of guanosine nucleotides within T and B lymphocytes. The compound, whether as mycophenolate mofetil or mycophenolic acid, hinders lymphocyte proliferation and the generation of antibodies triggered by various mitogens and antigens. Additionally, mycophenolate mofetil exhibits activity in numerous animal transplantation models, indicating a potential role in inhibiting the chronic rejection process.*

Keywords: tacrolimus, liver transplantation, efficacy, immunosuppression

I. INTRODUCTION

Catharanthus In 1982, our research program at Syntex, Palo Alto, commenced on immunosuppressive drugs. The initiative drew from our prior work with cyclosporin A (CsA) and purine synthesis in lymphocytes, as well as Syntex chemists' expertise in synthesizing anti-inflammatory and immunosuppressive compounds like fluorinated glucocorticoids. Following Borel et al.'s discovery in 1976 that CsA inhibits T-lymphocyte responses in rodents, our team demonstrated its suppression of human T-lymphocytic responses (Leoni et al., 1978). Administering CsA orally to rabbits, we achieved donor-specific tolerance to kidney allografts (Green and Allison, 1978; Green et al., 1979). Pioneering the use of CsA for bone marrow transplantation, we established long-term blood cell chimerism post-treatment termination (Tutschka et al., 1979). Simultaneous work in Calne et al.'s labs underscored CsA's efficacy in preventing organ graft rejection in various animal models, paving the way for clinical trials and the development of a transplantation regimen involving CsA, azathioprine (AZA), and a glucocorticoid. Mycophenolate mofetil (MMF) stands out as the primary immunosuppressant for alleviating calcineurin inhibitor (CNI)-related complications due to its low toxicity. Beyond this, MMF exhibits a CNI-sparing effect, effectively diminishing the risk of acute rejection or graft failure. However, the use of MMF comes with drawbacks, including leukopenia and gastrointestinal (GI) issues like vomiting, diarrhea, and abdominal pain. These complications often necessitate a reduction in the MMF dosage. While the KFDA deemed the My-Rept 500 mg tablet equivalent to the Cellcept 500 mg capsule, no clinical studies have explored the efficacy and safety of the tablet formulation in liver transplant (LT) patients using My-Rept. Consequently, our investigation delved into comparing the efficacy and safety profiles of the tablet and capsule forms of mycophenolate mofetil (MMF) in individuals who had undergone liver transplantation.

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HISTORY

Mycophenolate mofetil, part of the mycophenolic acid drug class, traces its roots over 120 years when scientists first isolated mycophenolic acid from a Penicillium byproduct, utilizing it as an antibacterial and antifungal agent in 1896. During the 1960s, mycophenolic acid found application as an anticancer drug. Fast forward to 1995, Mycophenolate mofetil gained FDA approval for preventing acute rejection in kidney transplantation. Beyond transplantation, subsequent research unveiled its effectiveness in treating autoimmune conditions such as lupus nephritis, vasculitis, and dermatomyositis. Launched in China in 1997, Mycophenolate mofetil's efficacy and safety have been extensively validated through two decades of clinical practice.

MECHANISM OF ACTION

The Mycophenolate's active metabolite, mycophenolic acid (MPA), inhibits T-cell and B-cell proliferation, along with suppressing the generation of cytotoxic T-cells and antibodies. Additionally, MPA hinders lymphocyte and monocyte adhesion to endothelial cells in blood vessels, a process integral to inflammation, by glycosylating cell adhesion molecules[1]Allison AC, Eugui EM: Purine metabolism and immunosuppressive effects of mycophenolate mofetil (MMF). Clin Transplant. 1996 Feb;10(1 Pt 2):77-84. [Article]Inhibiting inosine 5'-monophosphate dehydrogenase enzyme (IMPDH), mycophenolic acid (MPA) selectively hampers IMPDH II, thereby impeding de novo purine biosynthesis that fosters immune cell proliferation.(2)Park H: The emergence of mycophenolate mofetilin dermatology: from its roots in the world of organ transplantation to its versatile role in the dermatology treatment room. J Clin Aesthet Dermatol. 2011 Jan;4(1):18-27. [Article]Typically, inosine monophosphate (IMP) undergoes transformation into xanthine monophosphate (XMP) by IMPDH. XMP serves as a metabolite crucial for the synthesis of guanosine triphosphate (GTP)(3)Villarroel MC, Hidalgo M, Jimeno A: Mycophenolate mofetil: An update. Drugs Today (Barc). 2009 Jul;45(7):521-32. doi:10.1358/dot.2009.45.7.1384878. [Article]Allison AC: Mechanisms of action of mycophenolate mofetil. Lupus. 2005;14 Suppl 1:s2-8. [Article]Sagcal-Gironella AC, Fukuda T, Wiers K, Cox S, Nelson S, Dina B, Sherwin CM, Klein-Gitelman MS, Vinks AA, Brunner HI: Pharmacokinetics and pharmacodynamics of mycophenolic acid and their relation to response to therapy of childhood-onset systemic lupus erythematosus. Semin Arthritis Rheum. 2011 Feb;40(4):307-13. doi: 10.1016/j.semarthrit.2010.05.007. Epub 2010 Jul 23. [Article]GTP plays a crucial role in synthesizing RNA, DNA, and proteins. Consequently, mycophenolate mofetil disrupts the de novo production of guanosine nucleotides, hindering the synthesis of DNA, RNA, and proteins essential for immune cell production.(4)Park H: The emergence of mycophenolate mofetilin dermatology: from its roots in the world of organ transplantation to its versatile role in the dermatology treatment room. J Clin Aesthet Dermatol. 2011 Jan;4(1):18-27. [Article]In addition to the aforementioned anti-inflammatory effects, MMF induces a reduction in tetrahydrobiopterin levels. This leads to diminished activity of the inducible nitric oxide synthase enzyme, subsequently lowering the production of peroxynitrite—a molecule that fosters inflammation.(5)Srinivas TR, Kaplan B, Meier-Kriesche HU: Mycophenolate mofetil in solid-organ transplantation. Expert Opin Pharmacother. 2003 Dec;4(12):2325-45. doi: 10.1517/14656566.4.12.2325 . [Article]

METABOLISM

Upon oral and intravenous administration, mycophenolate mofetil undergoes complete metabolism by liver carboxylesterases 1 and 2, resulting in the formation of mycophenolic acid (MPA), the active parent drug. Subsequently, the enzyme glucuronyl transferase further metabolizes MPA, generating the inactive phenolic glucuronide of MPA (MPAG). (1)FDA label, Mycophenolate mofetil [Link]Significantly, the glucuronide metabolite undergoes conversion to MPA through enterohepatic recirculation. Mycophenolate mofetil, evading metabolism in the intestine, enters the liver via the portal vein and undergoes transformation into the pharmacologically active MPA within liver cells.(2)Lamba V, Sangkuhl K, Sanghavi K, Fish A, Altman RB, Klein TE: PharmGKB summary: mycophenolic acid pathway. Pharmacogenet Genomics. 2014 Jan;24(1):73-9. doi: 10.1097/FPC.0000000000000010. [Article]Additional metabolites of MMF, namely N-(2-carboxymethyl)-morpholine, N-(2-hydroxyethyl)-morpholine, and the N-oxide segment of N-(2-hydroxyethyl)-morpholine, arise in the intestine due to the activity of liver carboxylesterase 2.(3)Lamba V, Sangkuhl K, Sanghavi K, Fish A, Altman RB, Klein TE: PharmGKB summary: mycophenolic acid pathway. Pharmacogenet Genomics. 2014 Jan;24(1):73-9. doi: 10.1097/FPC.0000000000000010.

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[Article]FDA label, Mycophenolate mofetil [Link]The primary enzymes involved in MPA metabolism within the liver include UGT1A9 and UGT2B7, with other UGT enzymes contributing as well. This metabolic process gives rise to four major MPA metabolites: 7-O-MPA-β-glucuronide (MPAG, inactive), MPA acyl-glucuronide (AcMPAG) formed through uridine 5′-diphosphate glucuronosyltransferases (UGT) activities, 7-O-MPA glucoside produced via UGT, and minimal quantities of 6-O-des-methyl-MPA (DM-MPA) mediated by CYP3A4/5 and CYP2C8 enzymes.(4)Park H: The emergence of mycophenolate mofetilin dermatology: from its roots in the world of organ transplantation to its versatile role in the dermatology treatment room. J Clin Aesthet Dermatol. 2011 Jan;4(1):18-27. [Article]

ROUTE OF ADMINISTRATION-

Less than 1% of the drug is excreted as MPA in urine. In a pharmacokinetic study with oral administration of mycophenolate mofetil, 93% is excreted in urine, and 6% in feces. An inactive metabolite, MPAG, accounts for approximately 87% of the entire administered dose excreted in urine.

HALF LIFE

After oral administration, the average apparent half-life of mycophenolate mofetil is 17.9 (±6.5) hours, while after intravenous administration, it is 16.6 (±5.8) hours.

TOXICITY

In rats, the oral LD50 for mycophenolate mofetil is 250 mg/kg, while in mice, it exceeds 4000 mg/kg.

OVERDOSE

Acute overdose may manifest with hematological abnormalities such as leukopenia and neutropenia, along with gastrointestinal symptoms.

USE-Utilized in conjunction with other drugs, mycophenolate prevents your body from rejecting a transplanted organ (e.g., kidney, liver, heart). Categorized as an immunosuppressant, it operates by diminishing your immune system's defenses to facilitate the acceptance of the new organ as part of your own body.

SIDE EFFECT-

- Constipation
- Nausea
- Headache
- Diarrhea
- Vomiting
- Stomach upset
- Gas
- Tremor
- Dizziness
- Drowsiness
- Trouble sleeping

PHARMACODYNAMIC

Mycophenolate mofetil serves as a prodrug, transforming into mycophenolic acid (MPA). MPA, the active form, inhibits the proliferation of immune cells and the generation of antibodies responsible for transplant rejection. This mechanism enhances the success rates of transplantation, mitigating the detrimental consequences of graft rejection.(1)Allison AC: Mechanisms of action of mycophenolate mofetil. Lupus. 2005;14 Suppl 1:s2-8. [Article]

PRECAUTION

Reproductive Toxicity:

Mycophenolate mofetil poses reproductive toxicity, elevating the risk of miscarriage and congenital malformations. Women of childbearing age on this medication should employ contraception.

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Pregnancy Planning:

Patients intending to become pregnant should notify their doctor at least 6 months in advance. Mycophenolate mofetil should be avoided during pregnancy.

Immune Suppression:

Mycophenolate mofetil partially suppresses the body's immune response, increasing the susceptibility to infections. Consequently, active vaccines should not be administered during the treatment process.

II. CONCLUSION

The study indicates that the newly formulated tablet could serve as an effective treatment, ensuring steady systemic exposure to MMF. This may contribute to lowering the risk of graft failure in liver transplant recipients.

REFERENCES

[1]. Mycophenolate mofetil, azathioprine and tacrolimus: mechanisms in rheumatology. Broen JC, van Laar JM. Nat Rev Rheumatol. 2020;16:167–178. - PubMed

[2]. Mycophenolate mofetil and its mechanisms of action. Allison AC, Eugui EM. Immunopharmacology. 2000;47:85–118. - PubMed

[3]. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. Ginzler EM, Dooley MA, Aranow C, et al. N Engl J Med. 2005;353:2219–2228. - PubMed

[4]. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. Appel GB, Contreras G, Dooley MA, et al. J Am Soc Nephrol. 2009;20:1103–1112. - PMC - PubMed

[5]. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial. Houssiau FA, D'Cruz D, Sangle S, et al. Ann Rheum Dis. 2010;69:2083–2089. - PMC - PubMed

[6]. Mycophenolate mofetil in systemic lupus erythematosus: efficacy and tolerability in 86 patients. Pisoni CN, Sanchez FJ, Karim Y, et al. https://pubmed.ncbi.nlm.nih.gov/15940766/ J Rheumatol. 2005;32:1047–1052. - PubMed

[7]. Mycophenolate mofetil is effective in reducing disease flares in systemic lupus erythematosus patients: a retrospective study. Nannini C, Crowson CS, Matteson EL, Moder KG. Lupus. 2009;18:394–399. - PubMed

[8]. Impact of race and ethnicity in the course and outcome of systemic lupus erythematosus. González LA, Toloza SM, Alarcón GS. Rheum Dis Clin North Am. 2014;40:433-54, vii-viii. - PubMed

[9]. Long-term follow-up of the MAINTAIN Nephritis Trial, comparing azathioprine and mycophenolate mofetil as maintenance therapy of lupus nephritis. Tamirou F, D'Cruz D, Sangle S, et al. Ann Rheum Dis. 2016;75:526–531. - PMC - PubMed

[10]. Long-term study of mycophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis. Chan TM, Tse KC, Tang CS, Mok MY, Li FK. J Am Soc Nephrol. 2005;16:1076–1084. - PubMed

[11]. Longterm followup after tapering mycophenolate mofetil during maintenance treatment for proliferative lupus nephritis. Laskari K, Tzioufas AG, Antoniou A, Moutsopoulos HM. J Rheumatol. 2011;38:1304–1308. - PubMed

[12]. Factors associated with relapse of lupus nephritis: a single center study of 249 cases. Hajji M, Harzallah A, Kaaroud H, Barbouch S, Hamida FB, Abdallah TB. Saudi J Kidney Dis Transpl. 2017;28:1349–1355. - PubMed

[13]. Can we identify who gets benefit or harm from mycophenolate mofetil in systemic lupus erythematosus? A systematic review. Mendoza-Pinto C, Pirone C, van der Windt DA, Parker B, Bruce IN. Semin Arthritis Rheum. 2017;47:65–78. - PubMed

[14]. A.C. AllisonImmunosuppressive drugs: the first 50 years and a glance forward Immunopharmacology(2000)A.C. Allison et al.

[15]. Immunological observations on patients with the Lesch–Nyhan syndrome, and on the role of de novo purine synthesis in lymphocyte transformationLancet(1975)R.A. Blaheta et al.

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[16]. Mycophenolate mofetil impairs transendothelial migration of allogeneic CD4 and CD8 T-cellsTransplant. Proc.(1999)W.A. Briggs et al.

[17]. Successful mycophenolate mofetil treatment of glomerular diseaseAm. J. Kidney Dis.(1998)N.P. Chanaud et al.

[18]. Inhibition of experimental autoimmune uveoretinitis by mycophenolate mofetil, an inhibitor of purine metabolismExp. Eye Res.(1995)D. Corna et al.

[19]. Mycophenolate mofetil limits renal damage and prolongs life in murine lupus autoimmune diseaseKidney Int.(1997)A.H. Enk et al.

[20]. Treatment of relapsing idiopathic nodular panniculitis (Pfeiffer–Weber–Christian disease) with mycophenolate mofetilJ. Am. Acad. Dermatol.(1998)L.D. Fairbanks et al.

[21]. Importance of ribonucleotide availability to proliferating T-lymphocytes from healthy humans. Disproportionate expansion of pyrimidine pools and contrasting effects of de novo synthesis inhibitorsJ. Biol. Chem.(1995)C.K. Fujihara et al.

[22]. Mycophenolate mofetil attenuates renal injury in the rat remnant kidneyKidney Int.(1998)R.C. Garcia et al.

[23]. Control of phosphoribosyl pyrophosphate synthesis in human lymphocytesBiochem. Biophys. Res. Commun.(1977)E.R. Giblett et al.

[24]. Adenosine deaminase deficiency in two patients with severely impaired cellular immunityLancet(1972)