Antiproliferatives and Transplantation

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Contents

Abstract

Antiproliferative agents include Mycophenolic acid and Azathioprine (which is less commonly used unless in certain conditions). They were initially identified for use in autoimmune and cancer research due to their role in disruption of cellular replication. They have now become the cornerstone of antirejection maintenance therapy in solid organ transplant. In this chapter we will describe the major times that lead to discovery, mechanisms of action, side effects, use during pregnancy and the major clinical trials.

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Antiproliferatives · Azathioprine · Clinical trials · Discovery · Mechanism of action · Mycophenolic acid · Side effects

1 Discovery

The antiproliferative medications azathioprine and mycophenolic acid (MPA) were both first identified as part of research into autoimmune diseases and cancer signaling pathways in humans. Before the structure of DNA was elucidated, a research team led by Gertrude B. Elion and George H. Hitchings studied an extensive number of purine analogs in the hope that they could discover a compound that could interrupt cellular replication (Elion 1989). In 1951, this team first synthesized 6-mercaptopurine (6-MP) which was initially approved for use in the treatment of childhood leukemias (Elion et al. 1960).

Meanwhile, after several advances were made in understanding the immunologic basis of organ transplantation and rejection, a separate team led by Sir Roy Calne began to use 6-MP in experimental attempts at human kidney and heart transplants (Schwartz et al. 1958). Elion and Hitching later synthesized a metabolic derivative of 6-MP in 1957 named *BW 57-322*, later termed azathioprine (Elion 1989). In collaboration with Elion and Hitching, Calne began to use azathioprine in place of 6-MP due to its more favorable side-effect profile. In 1954, the first successful living kidney transplant between identical twins was performed in Boston by Joseph Murray and his team. This work contributed to receiving the Nobel Prize for Medicine later on. In 1962, Calne and his team utilized an immunosuppressive regimen of azathioprine and glucocorticoids to perform the first successful long-term kidney transplantations from non-related donors (Murray et al. 1963).

Mycophenolic acid (MPA) was first synthesized in the late nineteenth century by an Italian medical scientist Bartolomeo Gosio. Using samples collected from spoiled corn, he discovered the fungal species *Penicillium brevicompactum* which had considerable antibacterial activity. In 1896, he isolated the crystallized form of the compound which gave the fungus its antibacterial properties (Zhang and Demain 2005). His discovery was initially forgotten until two American scientists, C.L. Alsberg and O.M. Black, later synthesized the same compound in 1912, giving it the name mycophenolic acid (Regueira et al. 2011).

MPA was initially used for its antibacterial and antiviral effects, though its adverse side-effect profile led to its near abandonment in clinical use. This changed in the 1980s due to the research of South African geneticist Anthony Allison and his wife Elsie Eugui. Allison discovered the metabolic pathway of de novo guanine nucleotide biosynthesis, particularly the enzyme Inosine-5'-monophosphate dehydrogenase (IMPDH), which is partly responsible for immune rejection in organ transplantation.

In their search for a molecule that could block this pathway, the Allisons experimented with the neglected antibacterial agent MPA, which they found to have significant immunosuppressive activity in mice and strong inhibition of mitogenic stimulation of human lymphocytes (Bentley 2000). After working to synthesize variants with less toxicity and increased immunosuppressive effect, they went on to demonstrate that MPA was useful in animal models of organ transplantation which was later extrapolated to humans in clinical trials (Bechstein et al. 1992; Taylor et al. 1994). MPA was then approved for use in kidney transplantation by the FDA in May of 1995 under the brand name CellCept®.

2 Mechanism of Action

2.1 Azathioprine

Although azathioprine is no longer used routinely in solid organ transplantation protocols, it was one of the first immunosuppressive agents in the field. Currently use is limited to stable patients already on therapy, those intolerant to mycophenolate acid due to GI side effects, or female transplant recipients considering pregnancy.

Azathioprine is a purine analog prodrug, which is rapidly hydrolyzed to 6-mercaptopurine (6-MP) after administration. 6-MP is later converted by hypoxanthine guanine phosphoribosyl transferase (HGPRT) to various metabolites including active 6-thioguanine (6-thioGTP), which becomes incorporated into actively replicating DNA preventing the de novo pathway of purine synthesis (Maltzman and Koretzky 2003). More specifically, 6-thioGTP has been shown to prevent DNA synthesis in actively replicating T cells. Thiopurine S-methyltransferase (TPMT) methylates 6-MP into the inactive form 6-methylmercaptopurine (6-MMP) (Fig. 1).

Recently, the same compound has been shown to inhibit CD28, a co-stimulatory mediator essential for the signaling pathway required for T cell activation (Aarbakke et al. 1997). Related metabolites of azathioprine have also demonstrated inhibition of the enzyme Rac-1, which sets in motion a series of pathways that culminate with mitochondrial-driven T cell apoptosis (Poppe et al. 2006). In TPMT enzyme deficient patients, toxic levels of 6-thioGTP can accumulate leading to life-threatening myelosuppression. Hence TMPT genotyping is recommended prior to initiation of azathioprine (Relling et al. 2013).

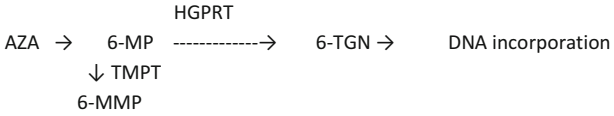

Fig. 1 Pharmacokinetics of MMF. *AZA* Azathioprine, *6MP* 6-Mercaptopurine, *HGPRT* Hypoxanthine guanine phosphoribosyltransferase, *6TGN* 6-Thioguanine nucleotides, *TMPT* Thiopurine S-methyltransferase, *6-MMP* 6-methylmercaptopurine

2.2 Mycophenolic Acid

MPA is a reversible inhibitor of Inosine monophosphate dehydrogenase IMPDH, a crucial enzyme in the de novo biosynthesis of guanine nucleotides. Mycophenolate mofetil (MMF, brand name CellCept®) undergoes rapid hydrolysis to the active form MPA after administration (Ransom 1995). The mean half-life of MPA in systemic circulation is approximately 17 h. MPA is mainly metabolized by the liver, undergoes glucuronidation to a pharmacologically inactive 7-O-glucuronide metabolite (MPAG) (major metabolite) and active metabolite MPA-acyl-glucuronide (AcMPAG) which is responsible for the GI toxic effects (Jeong and Kaplan 2007).

It undergoes enterohepatic circulation which contributes to approximately 35% of the MPA area under the curve (AUC). This leads to a secondary plasma peak after 6–12 h from administration. Cyclosporin inhibits this enterohepatic pathway for MPA lowering overall MPA plasma levels. MPA is eventually excreted through the kidneys (Jeong and Kaplan 2007) (Fig. 2).

While most cells in the human body can recover guanine nucleotides through salvage pathways, proliferating lymphocytes are entirely dependent upon the IMDPH pathway for purine synthesis and thus DNA replication (Ji et al. 2006). This partial selectivity for lymphocyte proliferation accounts for MPA's superior side-effect profile and efficacy when compared to azathioprine. MPA has been shown in in vivo experiments to block both T and B cell proliferation, and to down-regulate the expression of adhesion molecules on lymphocytes (Ensley et al. 1993).

3 Optimal Dose of Mycophenolic Acid

Clinical trials were conducted to assess optimal dosage, when comparing 2 g/day versus 3 g/day there was no additional benefit shown and a trend to more side effects with the higher dose, rendering 2 g/day as the standard of care. (Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection. European Mycophenolate Mofetil Cooperative Study Group 1995).

4 Enteric-Coated Mycophenolic Acid

In an effort to reduce the gastrointestinal side effects of MMF, enteric-coated mycophenolate sodium (EC-MPS) was developed. This formulation allows for delayed release of MPA in the small intestine. Clinical trials showed similar safety profiles and efficacy including similar rates of biopsy proven rejection, graft loss,

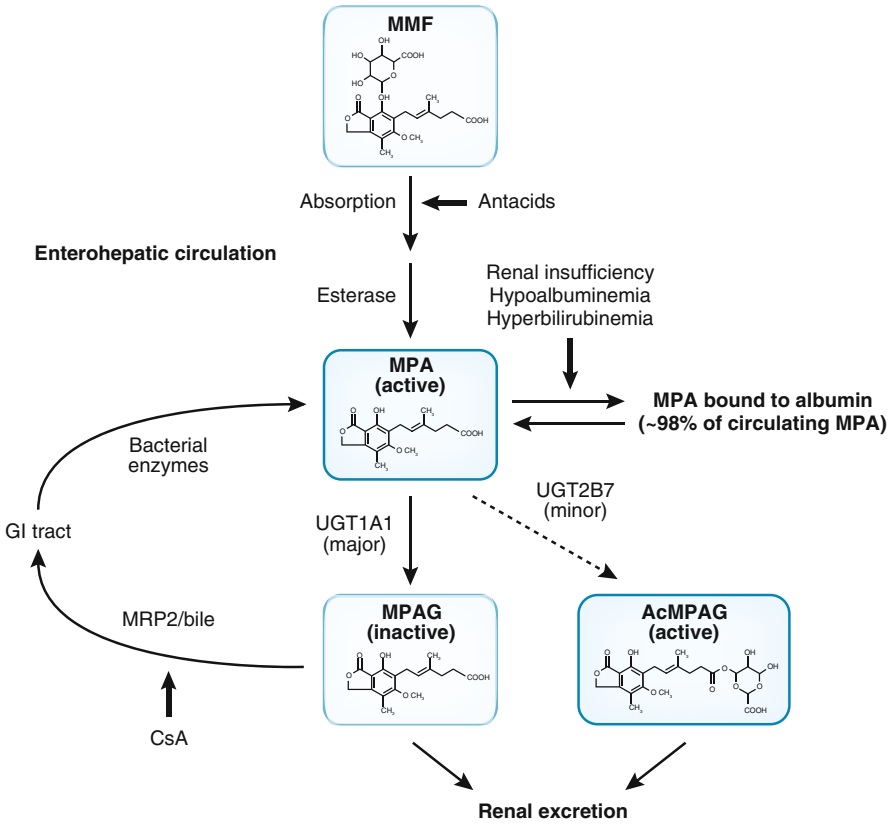

Fig. 2 Pharmacokinetics of MMF. *MMF* Mycophenolate mofetil, *MPA* Mycophenolic acid, *MPAG* inactive 7-O-glucuronide metabolite, *AcMPAG* active metabolite MPA-acyl-glucuronide. From "Therapeutic Monitoring of Mycophenolate Mofetil" by Hyunyoung Jeong and Bruce Kaplan. CJASN January 2007, 2 (1) 184–191. Reprinted with permission

and death. However, gastrointestinal adverse events were also found to be similar (Salvadori et al. 2004).

5 Target Dose Monitoring of MMF

Clinical trials showed a strong association of MPA concentration with incidence of rejection and individual variation of MPA AUC and pre-dose concentration, which led some to advocate for target dose monitoring of MMF (Jeong and Kaplan 2007). However, subsequent prospective clinical trials showed no significant difference in

biopsy proven acute rejection and graft loss in the fixed dose of MMF compared to concentration controlled arm. Also elevated MPA levels could not be correlated to its toxic effects. With the similar outcomes and extra expenses, routine target dose monitoring has fallen out of favor (Byrne et al. 2011).

6 Side Effects

The relatively rapid cellular turnover in the gastrointestinal tract and bone marrow accounts for their particular susceptibility to the side effects of antiproliferative medications. The most substantial side effect of azathioprine is bone marrow suppression (anemia, thrombocytopenia, and leukopenia), which is why regular monitoring with complete blood counts is essential. Dose reduction may be helpful and improvement in the CBC can be seen as soon as 7–10 days after adjustment (Maltzman and Koretzky 2003). Pancreatitis and hepatotoxicity are less rare but more serious side effects reported with azathioprine (Aarbakke et al. 1997).

As mentioned previously, MPA is more specific for proliferating lymphocytes than azathioprine and as such bone marrow suppression is far less common (Bunnapradist and Ambühl 2008). GI upset, particularly nausea, vomiting, and diarrhea are the most common side effects associated with MPA and may lead to a decreased dosage in many patients. Some studies have shown that utilizing enteric-coated mycophenolate sodium instead of MMF may lead to less GI side effects and higher sustained doses overtime (Ortega et al. 2011).

7 MMF and Azathioprine During Pregnancy

Several prospective and large case series have suggested safety of azathioprine use during pregnancy without increase in malformations (Natekar et al. 2011). This remains one of the indications for use of azathioprine in heart transplantation.

In 2006 the national transplantation pregnancy registry NTPR reported increased risk of both miscarriages and birth defects and female transplant recipients using MPA during pregnancy. This did not appear to affect male recipients. In 2007 the Food and Drug Administration (FDA) issued a black box warning on the use of MPA during pregnancy. Pregnancy testing was also recommended immediately before initiation of MPA and at 8–10 days after use. In order to educate health providers in females receiving the truck with reproductive potentials, the FDA mandated a single shared risk evaluation and mitigation strategies (REMS) system in 2012 (Kim et al. 2013).

8 MMF vs Azathioprine

In the 1990s three pivotal trials compared MMF vs azathioprine based immunosuppression regimens, showing a reduction in incidence of acute rejection post renal transplantation from 40–45% to 20–25% (Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection. European Mycophenolate Mofetil Cooperative Study Group 1995; A blinded, randomized clinical trial of mycophenolate mofetil for the prevention of acute rejection in cadaveric renal transplantation. The Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group 1996; Sollinger 1995). A few years later the heart transplant community underwent its first large collaboration with a multicenter double-blind, active controlled trial randomizing 650 patients undergoing their first heart transplant to receive azathioprine vs MMF, in combination with cyclosporine and corticosteroids. There were significant reductions in one-year mortality, rejection with hemodynamic compromise and in treatable rejection episodes in the MMF cohort (Kobashigawa et al. 1998).

In an attempt to assess long-term effect of MMF on renal graft survival, the US renal transplant scientific registry was analyzed by Ojo et al. between October 1988 to June 1997 with a total of 66,774 renal transplant recipients, it showed at 4 years MMF reduced the relative risk of graft loss by 27% independent of incidence of acute rejection (Ojo et al. 2000). These trials have led to MMF being the cornerstone as an antiproliferative in solid organ transplant and its replacement of azathioprine.

9 Clinical Trials

Below are some highlighted clinical trials in solid organ transplant with MMF and/or azathioprine (Table 1):

In spite of the numerous clinical trials, there remains no single standardized immunosuppression regimen. Rather, they are individualized based on patient's characteristics, risk profiles, and underlying comorbidities and balancing the risks of over immunosuppression with the risk of rejection (Kobashigawa 2017).

Table 1 Major randomized clinical trials of antiproliferative medications in solid organ transplantation

Study	Comparison	Patients	Follow-up (years)	Survival	Rejection	Notes
Kidney						
European Renal MMF Study group, 1995 (Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection. European Mycophenolate Mofetil Cooperative Study Group 1995)	MMF 2G vs MMF 3G vs placebo (background of CSA + steroids)	491	0.5	No difference	Less with MMF at both doses (no difference between MMF doses)	
U.S. Renal MMF Study group, 1995 (Sollinger 1995)	MMF 2G vs MMF 3G vs AZA (background of CSA + steroids)	499	0.5	No difference	Less with MMF at both doses (no difference between MMF doses)	Use of antilymphocyte agents for rejection higher in AZA group
Tricontinental Renal MMF Study group, 1995 (A blinded, randomized clinical trial of mycophenolate mofetil for the prevention of acute rejection in cadaveric renal transplantation. The Tricontinental Mycophenolate Mofetil	MMF 2G vs MMF 3G vs AZA (background of CSA + steroids)	503	0.5	No difference	Less with MMF at both doses (no difference between MMF doses)	

Renal Transplantation Study Group 1996)						
Halloran, et al. (meta-analysis), 1997 (Halloran et al. 1997)	MMF 2G vs MMF 3G vs AZA or placebo (background of CSA + steroids)	1,493	1	No difference	Less with MMF at both doses (no difference between MMF doses)	No difference in graft survival between all groups
Shapiro et al. (1999)	TAC vs TAC + MMF (background of steroids)	206	1.5	No difference	Less with TAC + MMF group	
Johnson et al. (2000)	TAC + AZA vs TAC + MMF vs CSA + MMF	223	3	No difference	No difference (though trend towards lower rejection in TAC + MMF group)	CSA + MMF group with significantly worse renal function
Gonwa et al. (Prograf Study Group), 2003 (Gonwa et al. 2003)	TAC + MMF vs TAC + SRL	361	0.5	No difference	No difference	TAC + SRL group with significantly worse renal function
Hall et al. (the ERL B301 Study Group), 2004 (Salvadori et al. 2004)	EC-MPS vs MMF (background of Neoral + steroids)	423	1	No difference	No difference	Both safety profiles and GI adverse events were similar for both groups
MYSS, 2007 (Remuzzi et al. 2007)	MMF + CSA vs AZA + CSA	248	5	No difference	No difference	
Heart						
Kobashigawa et al. (1998)	MMF vs AZA	650	3	Higher with MMF	Less with MMF	Less CAV with MMF at 1 year, but more opportunistic infections
Eisen et al. (2003)	EVR 1.5G vs EVR 3G vs AZA (background of CSA + steroids)	634	1	No difference	No difference	EVR associated with less CAV but worse renal function

(continued)

Table 1 (continued)

Study	Comparison	Patients	Follow-up (years)	Survival	Rejection	Notes
Keogh et al. (2004)	AZA vs SRL	136	2	No difference	Less rejection with SRL at 6 months	SRL associated with less CAV, worse renal function more anemia, AZA with more nausea and arrhythmia
Kobashigawa et al. (2006)	TAC/MMF vs TAC/SRL vs CSA/MMF	343	1	No difference	Less treatable rejection in the TAC groups	TAC/MMF associated with better renal function, TAC/SRL associated with impaired wound healing
TICTAC trial, 2011 (Baran et al. 2011)	TAC vs TAC + MMF (background of early steroids)	150	1	No difference	No difference	No difference in CVA between groups
Eisen et al. (2013)	MMF + standard CSA vs EVR + reduced-dose CSA	721	2	No difference	No difference	EVR with less CAV than MMF, though high-dose EVR (3.0 mg) stopped prematurely due to increased mortality
SCHEDULE trial, 2016 (Andreassen et al. 2016)	MMF + CSA vs EVR + reduced-dose CSA with early CSA withdrawal	115	3	No difference	More mild rejection in EVR-only group, but no difference at 1 year	EVR with less CAV but more opportunistic infections
Liver						
Jain et al. (1998)	TAC vs TAC + MMF (background of steroids)	200	1	No difference	No difference	Trend towards decreased rejection and nephrotoxicity in MMF group

Klupp et al. (1999)	CSA + MMF vs TAC + MMF vs TAC (background of steroids)	120	1.5	TAC + MMF and TAC group with higher survival	TAC + MMF and TAC group with lower rejection	
Fischer et al. (2000)	MMF vs AZA (background of CSA + steroids)	63	1	No difference	Less with MMF	Bone marrow suppression less common with MMF
Wiesner et al. (2001)	MMF vs AZA (background of CSA + steroids)	565	1	No difference	Less with MMF at 6 months, no difference at 1 year	
Lung						
McNeil et al. (2006)	MMF vs AZA (background of CSA + steroids)	315	3	Significant 1 year survival with MMF, not significant at 3 years	No difference	
Strueber et al. (2016)	MMF vs EVR (background of CSA + steroids)	190	2	No difference	Less with EVR	High dropout rate reported in EVR group
Simultaneous pancreas/kidney						
Odorico et al. (1998)	AZA vs MMF (background of CSA + steroids)	109	2	No difference	Less with MMF	Similar reduction in rejection rates for both kidney and pancreas with MMF
Merion et al. (2000)	AZA vs MMF (background of CSA + steroids)	150	0.5	No difference	No difference	

AZA azathioprine, *MMF* mycophenolate mofetil, *EC-MPS* enteric-coated mycophenolate sodium, *CSA* cyclosporine, *EVR* everolimus, *TAC* tacrolimus, *SRL* sirolimus, *CAV* cardiac allograft vasculopathy, *sCr* serum creatinine

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