THE USE OF MYCOPHENOLATE MOFETIL

IN LIVER TRANSPLANT RECIPIENTS

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Abstract

Mycophenolate mofetil (MMF) is an important drug in the modern immunosuppressive arsenal. MMF is the semi-synthetic morpholinoethyl ester of mycophenolate acid (MPA). MPA prevents T and B cell proliferation by specifically inhibiting a purine pathway required for lymphocyte division. In this paper, the authors extensively reviewed the experience of MMF use in liver transplant recipients. In randomised trials, MMF decreased the rate of acute rejection after liver transplantation, without a significant increase of septic complications. However, to date, there is no data indicating that MMF increases liver transplant patient or graft survivals. MMF is interesting for its particular side-effects profile that is very different from the other immunosuppressants. The absence of MMF nephrotoxicity is of specific interest in liver recipients with impairment of renal function. Monitoring of MPA AUC might be interesting to limit side effects and provide better clinical efficacy, but the exact role of MPA monitoring in liver recipients has still to be further evaluated in large series.

Keywords:

Liver Transplantation; Immunosuppression; Review; Side effects; Adult; Children; kidney; transplantation; solid organ; therapy; Surgery; rescue therapy; nephrotoxicity; Mycophenolate mofetil

1. Introduction

Results of solid organ transplantation have significantly improved in the last two decades, due to better indications, better surgical expertise and better immunosuppressive protocols. Particularly in liver transplantation (LT), excellent post transplant survival rate and quality of life have been achieved and LT is now the gold standard of care for many end-stage liver diseases. However, there is still place for significant improvements. Acute liver allograft rejection episodes remain frequent in the early postoperative period (about 20 to 50% depending on the immunosuppressive protocol), but most are easily manageable. Septic complications, promoted by immunosuppression and by the pretransplant recipient disabilities, are the leading cause of early post transplant morbidity and mortality. On the long term, side effects of the immunosuppressive therapies remain a major concern. New immunosupressive drugs with less toxicity are therefore of great interest.

2. Available immunosuppressive agents

There are basically four classes of immunosupressive drugs used at a large scale in organ transplantation in 2003. The first group is constituted of antibodies directed against some proteins of the lymphocyte membranes. Some antibodies are polyclonal and are produced by immunizing animals such as horses and rabbit with human lymphoid tissue (as antithymocyte globulin, ATGAM, Upjohn, or Thymoglobulin, Pasteur Mérieux, or ATG, Fresenius). Some are monoclonal (muromonab-CD3 orthoklone OKT3, Ortho Biotech). The most recent monoclonal antibodies are humanised and are directed against the lymphocyte IL2 receptor (daclizumab, Zenapax, Roche or basiliximab, Simulect, Novartis). Both may be used for induction therapy, and poly-clonal antibodies may be used as rescue for refractory rejections. Poly-clonal antibodies are very powerful immunosuppressants and have major impact on the susceptibility of the organ recipients to opportunistic infections. Monoclonal antibodies have a much more selective effect on rejection prevention, and do not increase the rate of infectious

complications, but their use is limited to the perioperative period. Calcineurin inhibitors (CNI) constitute the second group. Cyclosporine (CsA) (Neoral, Novartis) and tacrolimus (TAC) (Prograf, Fujisawa) are the key drugs of long-term immunosuppression in solid organ transplantation, but have severe chronic side effects, as nephrotoxicity, systemic hypertension, dyslipemia, diabetes mellitus (TAC) or gingival hyperplasia and hirsutism (CsA). The drugs of the third group are antimetabolites that inhibit lymphocyte proliferation, as azathioprine (AZA) (Imuran, Glaxo Wellcome) and mycophenolate mofetil (MMF) (Cellcept, Roche), with myelosuppression and gastrointestinal disturbances (MMF), as their major side effect. Corticosteroids constitute the fourth class, and their side effects are multiple and severe if they are used at high dose, as systemic hypertension, skin dystrophicity, dyslipemia, hyperglycemia, decreased bone metabolism….

In the near future, new immunosuppressive drugs with other mechanisms of action, as sirolimus (Rapamune, Wyeth-Ayerst), FTY720 (Novartis) or leflunomide, may provide new and interesting perspective. Sirolimus recently gained approval for rejection prevention in renal transplantation. However the place of these new medications and their ideal combination regimens with the older ones, have still to be established, particularly in LT.

Nearly all immunosuppressive regimens after solid organ transplantation are based on a life long CNI therapy with various combinations of the other medications. These immunosuppressive regimens have to be very powerful during the first 3 to 6 months after transplantation, when the risk of acute rejection is the greatest. Just after transplant (induction therapy), most recipients receive a combination of CNI, steroids, and AZA or MMF, with or without antibody induction (quadruple or triple regimens, respectively). After a few months without rejection, the therapy may be adapted to lower side effects. However, solid organ recipients remain at risk of acute rejection for their whole life. Most recipients receive a life-long immunosupressive therapy of at least two drugs. There is a recent and clear trend to

decrease the power of these chronic regimens in order to decrease their side effects, with some protocols evaluating the possibility of lowering or interrupting the administration of the most toxic drugs, namely CNI and steroids.

Compared to other transplanted organs, liver grafts seem to be less immunogenic and are better "tolerated". Liver graft loss due to acute or chronic rejection is very rare, and most LT immunosuppressive regimens are much less powerful than for other solid organs. Nowadays antibody induction has been very rare in LT [1]; a large number of LT centres now limit the use of steroids to low doses during a few months, and some promote LT without steroids (steroid-free regimens) [1]. Others do not use lymphocyte inhibitors at all, or use them for the first few months. An evaluation of the modern LT immunosuppression was recently reported [1]. In 2001, among the 4,812 liver recipients performed in the United-States, about 85% received TAC as primary CNI; 48% received MMF and 3% AZA as anti metabolites; 12% received humanised anti-IL2R monoclonal antibodies as induction therapy, and 88 % of the 4,812 received steroids at discharge [1].

3. Metabolism of Mycophenolate mofetil

MMF has been developed and clinically evaluated in the 1990's. MMF is the semi-synthetic morpholineoethyl ester of its active component, mycophenolate acid (MPA) (Fig. 1). MPA, a product of a *Penicillium* fungus, was originally isolated in 1896 [2], and shown to have anti-neoplastic [3-6], anti-viral [4], anti-fungal [7], and immunosuppressive activity. MPA prevents T and B cell proliferation by inhibiting a purine pathway required for cell division. MPA selectively inhibits the function of inosine-monophosphate-dehydrogenase (IMPDH) and therefore the synthesis of guanosine monophosphate (GMP) from inosine monophosphate (IMP), a rate-limiting step in the biosynthesis of purines crucial to cell cycling in T and B lymphocytes. Consequently, MPA blocks the proliferation and clonal expansion of T and B lymphocytes, preventing antibody production and prevents the generation of cytotoxic T cells,

as well as other effector T cells. This inhibition of purine synthesis by MPA is specific to lymphocytes, as other cells but lymphocytes may use a salvage enzymatic pathway to synthesise GMP from guanine, and are therefore resistant to the effects of MPA and MMF. The complete details of these pathways are beyond the scope of this paper, and were recently and extensively reviewed [8].

After oral administration and absorption of MMF, the ester linkage is rapidly hydrolysed by hepatic esterases to yield MPA. MPA undergoes hepatic glucuronidation by glucuronosyl transferase to form mycophenolic acid glucuronide (MPAG) [9], an inactive metabolite which is secreted into the bile; glucuronidases from gut bacteria convert it back to MPA which is reabsorbed and recirculated. Greater than 90% of a dose of MMF is excreted in the urine as MPAG [10].

4. Pharmacokinetics of Mycophenolate mofetil

MPA pharmacokinetics after MMF administration were extensively evaluated mainly in kidney graft recipients [11]. These studies showed that the bioavailability of oral MPA from MMF is 94% [12], and that the maximum plasma concentration occurs about 2 hours after administration. The half-life of MPA is situated between 16.6 and 17.9 hours, with a clearance between 10.6 and 11.8 l/h. MMF is available both in capsules and in a liquid form, and the intravenous formulation showed efficacy at least equivalent to *per os* MMF without increased toxicity [13].

MPA pharmacokinetics present a great inter patient and intra patient variability after MMF administration. Interestingly, in some series of adult and paediatric kidney recipients, it has been demonstrated that the 12-hour dose interval MPA area under the concentration-time curve (AUC) may accurately estimate the risks for acute rejection and haematological side-effects [11,14-16]. However, to date, there is no clear MPA AUC level that may distinguish the patients who may develop acute rejection from those who may not, and there is no

recommendation for MPA monitoring in clinical solid organ transplantation. Data are even less precise and with lower statistical significance for the predose trough MPA concentration [14].

Investigations of MPA pharmacokinetics have also been conducted in adult and paediatric liver transplant recipients [17,18]. No studies yet showed a predictive value for risk of rejection with AUC or trough levels in liver transplant recipients [19]. Moreover, all studies showed wide inter patient variability in drug exposure measured by the 12-h dose-interval AUC or trough levels, and this variability was greater in liver transplant recipient when compared to recipients of other solid organs [14,19]. Particularly in liver recipients, many factors may influence MPA pharmacokinetics: decreased absorption in the gastrointestinal tract, inhibition on the enterohepatic cycling, inhibition of the transport of the primary phenolic metabolite, low albumin levels, decreased liver function, and the other concomitant medications. Several studies have shown that CsA lowers MPA concentrations, and this effect is attributed to an inhibition of the transport of MPAG into bile from hepatocytes and therefore to a decrease of the enterohepatic MPA cycling [20]. In one series of kidney recipients, it was demonstrated that trough concentrations of MPA significantly increases following discontinuation of CsA 6 months after transplant. In this series, MPA concentration at 9 months was twice the value in patients without CsA, compared to patients still on CsA, with no change of dose of MMF [21]. This effect was not reported with the use of TAC [20].

In serum, MPA is tightly bound to albumin. In stable transplant patients, the MPA free fraction ranges from 1 to 3% of total MPA [14,22]. As the *in vitro* effect of MPA is dependent of free MPA concentration [22], MPA free fraction and free MPA AUC determination may be interesting in liver transplant patients in the early post-transplant period [17] and in any patient with low serum albumin concentration and/or hyperbilirubinemia [14]. In the setting of chronic renal failure, total MPA AUC values are comparable to those in patients with

normal kidney function, but free MPA AUC values can rise as much as 5-fold, placing the patient at increased risk for toxicity [23,24]. Therefore MPA free fraction and free MPA AUC determination may also be highly interesting in LT patients with terminal renal failure [23,24]. It may also be interesting to monitor free and total MPA AUC in liver recipients with side effects apparently related to MMF administration, but it has still to be further correlated by clinical studies.

In some LT recipients, a T-tube may be temporarily placed in the extrahepatic bile ducts to drain the bile externally during the few first days after transplant. When the liver function is stable, the tube is clamped and the bile is allowed to return to the gut. T-tube clamping can increase the blood/plasma concentration of drugs, as CsA, by improved enterohepatic recycling. However, in one series studying the effects of T-tube clamping on (total and free) MPA and MPAG kinetics, there was no significant change of AUC and it was suggested that no dosing alterations of MMF is required after T-tube clamping [25]. Another particularity of liver recipients is the use of long term selective bowel decontamination by some transplant centres. This destruction of the bowel flora may influence the enterohepatic cycling of some drugs. In one study, it was demonstrated that in liver recipients, selective bowel decontamination decreased the enterohepatic cycling, and therefore the bioavailability, of MPA [26].

5. Mycophenolate mofetil clinical efficacy and use in liver recipients

MMF efficacy was first assessed in kidney transplantation. Renal allografts in dogs treated with MMF had markedly prolonged graft survival with no evidence of nephrotoxicity, hepatotoxicity or bone marrow suppression [27]. Later it was also demonstrated that MMF treatment could reverse acute rejection in renal allografts in dogs [28]. The results from these early studies demonstrated the efficacy of MMF in preventing and treating allograft rejection, providing the impetus for the initial trials of MMF in human organ transplantation. In human

renal transplantation, three randomised, double-blind, controlled trials demonstrated that MMF at 2 or 3 g/day is more effective than placebo or AZA, in combination with CyA plus a steroid, for prevention of acute rejection [29-31]. In addition, MMF treatment results in a significant reduction of graft loss due to acute rejection. However, patient or graft survival at 1 year was not improved by MMF in any of these studies [29-31]. Side effects of MMF were gastrointestinal symptoms (mainly diarrhoea), myelosuppression resulting in leukopenia, thrombocytopenia and anaemia, and tissue invasive cytomegalovirus (CMV) infections in the high dose group (3g/d) [29-31]. MMF was then approved by the US Food and Drug Administration for the prevention of acute rejection in renal transplantation in June 1995.

5.1: Mycophenolate mofetil in liver recipients: randomised trials

They have been three prospective, randomised trials studying the efficacy of MMF on prevention of acute rejection in liver transplant recipients. The first study was a single centre comparison of a double therapy of TAC and steroids with a triple therapy of TAC, steroids and MMF 2 g/day [32]. One hundred and seventy-five patients were included in both groups. In the intention-to-treat analysis, the rate of acute rejection in the first 3 months was significantly lower in the MMF group (28% versus 38.9%), but the overall rate of rejection at 1 year was not significantly different (38.9% in the MMF group, versus 45%). However the results of this study are difficult to analyse as there were a high number of patients (58%) who interrupted MMF for infection, myelosuppression, and/or gastrointestinal disturbances. Moreover, 38 patients in the double therapy group (TAC and steroids) received MMF for ongoing rejection, nephrotoxicity and/or neurotoxicity. Interestingly, the need for corticosteroids was less after 6 months in the MMF group, as well as a lower perioperative need for dialysis. In a second randomised, single centre study comparing a quadruple immunosuppression including induction with lymphocytes antibodies, CsA, steroids, and AZA versus MMF 2g/day, MMF treated patients (n=28) experienced less acute rejection

episodes (21.4% versus 44.8%), compared to AZA treated patients (n=29), without significant side effects [33]. About 30% of the patients had to terminate the use of the study drug in both groups.

A third randomised reported study on MMF in LT was a multicentre trial consisting of 565 patients randomised to CsA, steroids and AZA or MMF 3 g/day [34]. Rates of rejection were significantly lower with MMF (38.5%) than AZA (47.7%). Again, the withdrawal rate was high in this study for both groups, 45.3% for MMF and 47.4% for AZA. This multicentre trial allowed the approval of MMF by the US Food and Drug Administration for the prevention of acute rejection after LT in August 2000.

In conclusion from these prospective trials, it appears that MMF (2 g/day) is a efficient immunosuppressive drug that decreases the rate of acute liver rejection of 20 to 50% when compared to absence of MMF, or to AZA, without significant higher risk of severe infections. However, the liver graft and patient survival is not improved by the use of MMF. Moreover in 30 to 50% of the patients, MMF therapy had to be interrupted, due to myelosuppression, infections, or digestive side effects. But this rate of withdrawal was also high in all control groups and was not higher with MMF than with AZA. This may indicate that in most patients MMF 2g/day may be a too high dosing of the drug in LT recipients especially on TAC therapy. Interestingly, MMF treated patients required less steroid therapy and less need for dialysis [8].

5.2: Mycophenolate mofetil as rescue therapy in liver recipients

As MMF showed clear immunosuppressive effects, it was proposed to add MMF to liver recipients with chronic rejection as a rescue therapy before retransplantation. No randomised study has been published so far, but a few consecutive series were reported. In a series of 19 patients converted from AZA to MMF for chronic or refractory rejection, Hebert et al. from the University of California San Francisco Group, reported 14 patients with either complete or

partial histologic resolution and 3 with worsening [35]. This finding was also reported by other groups as Berlin [36-38], Pittsburgh [39], and Miami [40-42]. Thus MMF may be beneficial as a rescue therapy in liver transplant with refractory rejection, but this observation has to be proven by further controlled, randomised studies.

5.3: Mycophenolate mofetil for steroid withdrawal or elimination in liver recipients

As steroids have major side effects, some authors proposed that MMF use may allow steroid avoidance and proposed immunosuppressive regimens of MMF in combination with TAC without [43] or with antibody induction [44,45]. These studies showed that a bitherapy associating TAC and MMF without steroids might be efficient to prevent acute rejection in liver allograft recipients, as compared with protocols including corticoids. Steroid elimination is also possible in patients on CsA and MMF [46]. However there is not yet any proven beneficial effect of these steroid-free protocols in liver recipients in these studies.

5.4: Mycophenolate mofetil for calcineurin inhibitor toxicity in liver recipients

One of the main long-term complications of immunosuppression in LT recipients is renal impairment. In particular, many LT recipients enjoy long-term survival but develop progressive end-stage renal disease requiring dialysis and/or renal transplantation. Nephrotoxicity associated to CNI may be classified as acute or chronic; acute CNI nephrotoxicity occurs in the first weeks after transplantation, when the CNI blood levels are elevated. It is usually reversible after CNI dose reduction and is probably linked to impaired renal blood flow. In contrast, chronic nephrotoxicity is observed in the long-term course after transplantation. This toxicity can occur even with low CNI blood levels [47] and is mainly linked to irreversible structural renal changes [48]. With experience, transplant physicians learned to use much lower dose of immunosuppressive drugs, lowering the rate and the severity of their side effects. But progressive lowering of the CNI dosing induces a significant reduction of immunosuppression and higher risk of rejection. Some authors proposed to lower

CNI dosing in combination with introduction of MMF [38,49-53]. These non-randomised series showed some efficacy in improvement of renal function without high risk of rejection. Some authors went even further and proposed CNI withdrawal and MMF monotherapy. This was successfully reported in prospective non-controlled consecutive series [48,52,54-56]. In all these series, most patients were stable liver recipients with long follow-ups after transplantation without rejection, and most tolerated MMF monotherapy with significant improvement of renal function without severe rejection. When rejection occurred it was controlled by CNI reintroduction with or without steroid boluses. Recently a randomised series of 30 patients showed a significant reduction of serum creatinine, of systemic blood pressure, and of uric acid in the MMF monotherapy group [57]. However CNI was reintroduced in one third of patients for MMF side effects or acute rejection (3 among 14 patients on MMF therapy). These results have to be balanced with another randomised study that had to be interrupted because of a high rate (3/5) of rejection in the MMF monotherapy group, and because 2 of these patients had to be transplanted for ductopenic rejection [58].

All these studies showed that some improvement of renal function might be observed after CNI withdrawal and MMF introduction in liver recipients. This finding might be in part explained by a possible chronic but reversible renal impairment due to CNI, added to the structural change of chronic CNI nephrotoxicity, e.g. vasomotor effects on arterioles comparable to the acute nephrotoxicity [48]. A direct MMF effect might also be evoked, by prevention of structural changes like glomerular sclerosis and interstitial fibrosis [59].

5.6: Mycophenolate mofetil for viral infections in liver recipients

MPA has shown to inhibit the *in vitro* replication of some viruses, as parainfluenza-3 virus, type B4 Coxsackie virus, Epstein-Barr virus [60], human hepatitis B virus (HBV) [61], herpes virus [62], and human immunodeficiency virus (HIV) [63]. However, to date, these *in vitro* data were not confirmed by clinical observations. In a small series of 4 patients with

lamivudine resistant HBV reinfection, no benefit was demonstrated under MMF therapy [64]. In hepatitis C virus (HCV) patients, it was suggested that the use of MMF might delay the recurrence and severity of HCV reinfection post liver transplantation. This effect might be due to MMF fibrogenesis inhibition rather than to its antiviral activity [65-67]. However this potential effect was not confirmed by a randomised study studying the effects of MMF on a large cohort of HCV patients (106 randomised patients, MMF versus no MMF) [68]. In summary despite promising *in vitro* results, the protective effects of MMF in LT recipients transplanted for viral diseases have not been confirmed by clinical data to date.

5.7: Mycophenolate mofetil in paediatric liver recipients

MMF (20 to 40 mg/kg/d) may also be used in paediatric transplant recipients. MMF use in children was first evaluated in paediatric renal recipients [69]. In LT paediatric recipients, MPA pharmacokinetics showed large variability, as in adults [18,70]. The administration of CsA increased MMF dosage requirements, compared to TAC [18,70]. MMF was also used with success as rescue therapy in a series of 19 children, with normalisation of the liver function tests and histology in 62% of patients. Thirty-two percents of the patients had significant side effects and had to reduce their dosing or interrupt the medication [71]. MMF was also successfully used for CNI nephrotoxicity in paediatric liver recipients [72]. From all these reports, one can conclude that MMF may be used in paediatric LT recipients with the same results and side effects as compared with adult recipients.

6. Mycophenolate mofetil side effects and tolerability in liver recipients

As all other immunosuppressants, MMF has major side effects, some being aspecific and others specific to MMF. All immunosuppressive drugs lower immunity and therefore increase the risks of viral and bacterial infections, and also the risks of cancer development. However, MMF demonstrated from randomised trials in renal transplantation that this risk is not very high when compared to AZA, the other antimetabolite that is much less potent in rejection

prevention. MMF is generally a well-tolerated drug after transplantation, lacking permanent organ toxicity or lipid abnormalities. The only difference in infectious complications after renal transplantation is the occurrence of tissue-invasive CMV in the MMF 3 g/d groups [8], meaning that this dose may be too elevated. In the randomised studies in liver transplant recipients, there was no more infectious or tumoral complications in the MMF groups when compared to AZA [32,34], and this results confirmed other non-randomised reports [73].

MMF is not nephrotoxic and has no effect on the lipid profile or other cardiovascular risk factors as systemic hypertension or diabetes mellitus. The principal complications are gastrointestinal as nausea, vomiting, abdominal pain and diarrhoea. These symptoms tend to resolve with the daily dose reduction [8]. However, in the randomised trials in LT recipients, there was no more difference in gastrointestinal symptoms between patients on AZA and MMF [34]. MMF may also induce myelosuppression, including leukopenia and anaemia, thrombocytopenia being less frequent. However these side effects are not more frequent than with AZA [8,34]. When MMF related bone-marrow suppression occurs, it is often observed 30 to 180 days after transplantation. Adverse effects generally improve approximately one week after MMF discontinuation [8]. More serious MMF complications as cholestasis, gastritis, pancreatitis, bowel perforation, have also been described but are rare [8].

7. Economical considerations

MMF is an expensive drug, being about six to seven times more expensive than AZA [74]. Therefore life-long combination therapy of MMF with CyA or TAC involves the chronic use of two expensive medications. Considering the lower risk of rejection therapy and dialysis, it was calculated that in renal transplant recipients MMF treated patients are likely to have slightly lower first year costs, compared with controls, indicating that MMF treatment is cost-effective in the first year after renal transplantation [75]. These cost-effectiveness studies are not available yet in liver recipients, to the authors' best knowledge, but should show similar

results, as randomised studies showed less dialysis requirement and less rejection episodes in the MMF groups [8].

8. Conclusion

MMF is a new potent immunosuppressive drug that decreases the rate of acute rejection after LT in children and adults, without a significant increase of septic complications. However, to date, there is no data indicating that MMF increases LT patient or graft survivals. Especially in LT recipients, MMF therapy interruption is frequent, as septic events often complicate LT recipient follow-ups. MMF is generally well tolerated in LT recipients and is interesting for its particular side-effects profile that is very different from the other immunosuppressants, mainly CNI and steroids. The absence of nephrotoxicity is of great interest in LT recipients with impairment of renal function, in which MMF therapy may allow CNI dosing reduction in most cases or even CNI discontinuation in some very stable patients. MMF may also be used as rescue therapy of liver graft with chronic rejection, but this effect should be studied in a prospective and controlled trial. Monitoring of MPA AUC might be interesting to limit side effects and provide better clinical efficacy, but the exact role of MPA monitoring in liver recipients has still to be further evaluated in large series.

9. Expert opinion

MMF is a very important drug in the modern immunosuppressive arsenal of physicians dealing with LT recipients. MMF allows early CNI dosing reduction both in newly transplanted and stable LT recipients, allowing a kidney sparing immunosuppressive therapy. MMF also allows an early discontinuation of steroid administration as early as the first weeks after LT, or even in some cases the total avoidance of steroid therapy after LT. The main problem with clinical MMF use is the absence of adequate monitoring. MPA kinetics showed a large variability, particularly in LT recipients. Trough levels are not useful in MPA monitoring, MPA AUC has not shown any interest in LT recipients to date, and MPA kinetics

showed a great variability according to serum albumin concentration, bilirubinemia or renal function.

The authors use in their daily clinical practice MMF as a part of the first line immunosuppressive therapy in LT recipients, in combination with CyA or TAC, and low dose steroids for a few weeks (triple therapy). As CyA administration lowers MPA concentration, the authors start with a dose of 1 g/d or 2 g/d of MMF according to the kind of CNI co-administrated, TAC or CyA respectively. Liquid MMF is administrated through the naso gastric tube as early as the first postoperative day, and by capsules as soon as possible. MMF dosing is adjusted according to clinical efficacy and side effects. MMF is temporarily interrupted in case of septic complication or leukopenia, and the dose may be increased in patients suffering from rejection. MMF therapy allows the use of CNI at infra therapeutic trough levels, sometimes at the limit of detection. MMF therapy may also allow CNI administration interruption in very stable LT recipients with severe impairment of renal function.

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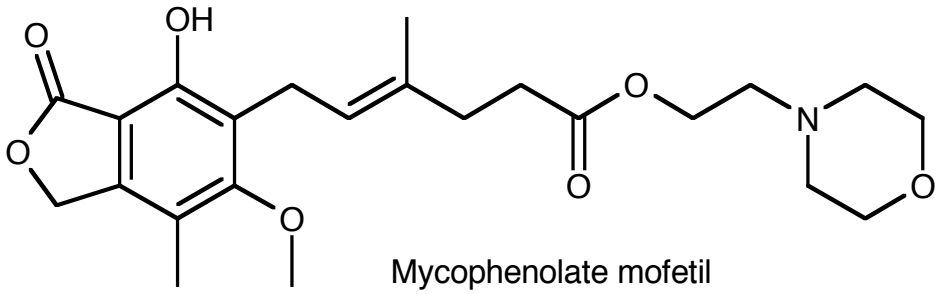
Figures

Fig 1: Chemical structure of Mycophenolate mofetil and Mycophenolic acid



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