EDITORIAL COMMENTS

Mycophenolate Mofetil in Transplantation

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Mycophenolate mofetil (MMF) blocks the de novo pathway of purine production in the lymphocytes and more specifically the production of guanocine by inhibiting the action of inosine monophosphate dehydrogenase[1]. The result of this action is the inhibition of T and B lymphocyte proliferation and the inhibition of antibody production by B lymphocytes[2-4].

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a. Mycophenolate mofetil in kidney transplantation

Immunosuppressive protocols with MMF, steroids and cyclosporine A (CsA) when compared with the triple drug immunosuppressive protocols of azathioprine (AZA), steroids and CsA were found to have 50% lower rate of acute rejection episodes[5-7], which is thought to be the basic cause of chronic allograft nephropathy[8-10]. The three – year patient and graft survival did not improve significantly[11,12] but the group of patients on 2 gr/d MMF when compared with the group of patients on AZA presented the following characteristics

a) Lower percentage of method failure (35% και 50% respectively),
b) Lower number of acute rejection episodes (16% και 36% respectively) and
c) Lower need of antilymphocyte antibodies for heavy acute rejection episodes[6].

There was a tendency for better graft survivals after a three-year follow up which was not statistically significant[6,11]. It has been shown that MMF can be used in combination with the polyclonal antilymphocyte antibodies. When ALG and MMF were used concomitantly there were statistically significant lower levels of IgG anti-ALG antibodies compared with the levels of IgG anti-ALG antibodies produced after the use of AZA with ALG[13].

In a recent retrospective analysis, the comparison of the effect of AZA and MMF on patient and graft survival by multivariate analysis, showed that the immunosuppressive protocol with MMF had significantly better results as far as patient and graft survival four years after the transplantation[14]. This favorable effect was present even in cases without a history of acute rejection episodes (in this study 66,774 patients, who received a renal allograft the period 1988-1997 were included). AZA was the basic immunosuppressant drug in 48,436 and MMF in 8,435 of them). The above findings are in accordance with both the experimental work[15] as well as with our experience[16].

It has been shown that MMF reduces the rate of acute rejection episodes in the pediatric population too[17]. This could result in better long-term function of renal allografts and greater duration of graft survival[18]. In an open prospective study, Jungraithmayr et al found that the triple drug immunosuppressive protocol with MMF and triple drug immunosuppressive protocol with AZA presented half-life graft survival in pediatric patients 29.4 years and 23.6 respectively[19].

The MMF toxicity is related with symptoms from the alimentary truck, the haematopoietic system and CMV infection. The triple drug scheme with MMF (dose 2 gr / d) when compared with the triple scheme with AZA presented significantly higher rate of gastroenterological toxicities (diarrhea, abdominal pain, nausea and vomiting), while there was no difference on the rate of leucopoenia which seems to be MMF dose related[11]. The heavy long lasting pancytopenias observed with AZA use are not observed with MMF (personal experience). As far as the matter of infections, there is a tendency for higher rate of infections of herpes virus group and specifically CMV infections[12].

Today, the MMF dose of 3 gr / d has been abandoned. The usual mean MMF dose is about 1.5 g / d

and it depends upon the age, the body surface area and the patient immunological status.

In summary MMF can be part of the triple drug basal immunosuppression of patients with a kidney graft from live or cadaveric donor or can replace the drug AZA in patients with declining graft function[16]. MMF allows lower doses of CsA limiting the toxic effect of the latter on the allograft or the steroid dose according to the existing problems (diabetes mellitus, bone disease or age).

b. Mycophenolate mofetil in heart transplantation

Until recently, the usual triple drug immunosuppressive scheme for heart transplantation was consisted from AZA, steroids and CsA[20]. MMF was used in heart transplantation after the successful experience in kidney transplantation. Initially, MMF was used to replace AZA in cases with mild rejection episodes of heart grafts. This use proved to be successful with reversal rejection rate of 73.3%[21]. Later MMF was proved to be effective in cases with relapsing acute rejection episodes diminishing significantly their frequency ($p=0.0001$)[22]. The usefulness of MMF was present even in late cases after transplantation diminishing the late rejection episodes[23]. A large randomized trial showed that the triple drug immunosuppressive scheme with MMF presented better results compared to the triple drug scheme with AZA in heart transplantation[24]. This trial was criticized for its protocol and for its results[25]. In a multicenter randomized trial there were no significant differences between AZA and MMF as far as the development of new coronary artery disease (CAD) or the evolution of preexisting CAD. In spite of this, the echocardiografic examination of the coronary arteries lumen showed, 12 months later, augmentation of the diameter of the lumen of patients taking MMF, while there was a decrease of the lumen diameter in the patients taking AZA. The three year follow up did not show significant difference in these parameters but the patients on MMF had better results in measured parameters separately when compared with those taking AZA. The patients on MMF had fewer lethal cardiovascular episodes and less atherosclerosis after heart biopsy. Finally the three-year survival was significantly higher in patients on MMF when compared with those who were on AZA ($p=0.0029$)[26]. In a recent large trial with a patent population of 5599 under triple drug immunosuppression (4942 on AZA and 657 on MMF) it was shown that the patients on MMF presented significantly better survival ($p=0.0012$)[27] after a three-year follow up. In this study, morbidity did not differ between two groups (infections, rejections, ejection fraction, heart graft angiopathy)[27]. It has been proposed that AZA replacement with MMF in patients with heart transplantation and renal failure, allows lower doses of CsA that lead to better renal function, without any change in the frequency of rejection episodes[28].

In pediatric heart transplantation MMF seems to be effective in reversal rejection and is connected with satisfactory profile of side effects. There is information suggesting that MMF may be significant in the basic immunosuppression for pediatric heart transplantation for prevention of heart rejection[29].

Recently it has been proposed that the measurement of MMF levels is useful, irrespective of age, in the prevention of heart rejection episodes during the first post - transplant year[30,31].

AZA and MMF present the less cardiovascular toxicity / danger compared with all the other immunosuppressive agents used in this field[27,32]. Both of them block purine synthesis but the action of MMF allows the selective inhibition of lymphocyte activation and proliferation. There are no elements to support that MMF contributes in the development of hypertension or causes abnormal lipid profil[32]. Also MMF has no diabetogenic action[32].

c. Mycophenolate mofetil in kidney – pancreas transplantation

Initially, CsA in combination with AZA and steroids were the cornerstone of therapy in simultaneous kidney – pancreas transplantation (SKPT) and were associated with an acute rejection rate of 85% or more[33-35]. The use of MMF instead of azathioprine has resulted in reduced rates of biopsy proven acute rejection[36]. Today, most pancreas transplant centers utilize quadruple drug immunosuppression, consisting of a monoclonal or polyclonal antibody agent for induction in combination with a calcinurin inhibitor, MMF and corticosteroids[33, 37-39]. Lately the use of antibody therapy has been questioned and the combination of MMF with tacrolimus without antibody has been used in an effort to avoid post – transplant morbidity and achieve reduced acute rejection rates[40].

d. Mycophenolate mofetil in liver transplantation

In a multicenter (22 international centers), controlled, double – blind randomized immediately after transplantation study the AZA and MMF efficacy was compared in a triple drug scheme (CsA and steroids). The number of primary liver recipi-

ents was 565 (278 on MMF). MMF was superior to AZA in preventing acute rejection at 6 months post transplantation. However the 1 – year graft and patient survival rates were equivalent between the two treatment groups, and the safety profiles between the two immunosuppressive agents were similar[41]. Reports concerning the use of MMF in combination with tacrolimus without steroids wait for further verification[42]. Early clinical trials suggest synergism of MMF with interferon alfa and MMF has been proposed as a possible antiviral agent because of its ribavirin – like effects[43]. Reasons for the potential beneficial effect of MMF could include a direct effect on HCV versus better suppression of rejection and reduced need for antirejection treatment. The results are contradictory in the literature[41,44,45].

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