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Mycophenolate mofetil embryopathy: A newly recognized teratogenic syndrome

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ABSTRACT

Mycophenolate mofetil (MMF) is probably the most common employed immunosuppressant drug in recipients of solid organ transplant and in many autoimmune diseases. In vitro studies, a significant number of single clinical observations and a recent study from a group of different European teratogen information services, have provided very consistent data supporting the existence of a specific MMF embryopathy. The typical malformative pattern of MMF embryopathy includes external ear anomalies ranging from hypoplastic pinna (microtia) to complete absence of pinna (anotia); cleft lip, with or without cleft palate, and ocular anomalies as iris or chorioretinal coloboma and anophthalmia/microphthalmia. Other less frequent features are congenital heart defects, distal limbs anomalies, esophageal atresia, vertebral malformations, diaphragmatic hernia, and kidney and central nervous system anomalies. Neurodevelopmental outcome seems favorable in the small number of patients where information about this issue is available, but neurological deficits have been documented. Physicians in charge of women under MMF therapy should be aware of the potential risk of this drug to cause a specific embryopathy and the need of interrupting the treatment at least six weeks before becoming pregnant.

1. Introduction

1.1. Mycophenolate mofetil: a very effective immunosuppressive drug

Mycophenolate mofetil (MMF), a pro-drug of Mycophenolic acid (MPA), is an immunosuppressive agent that was used for the first time in 1992 specifically in a group of kidney transplant recipients (Sollinger et al, 1992). In 1995 the use of MMF (CellCept®) (CellCept Product information 2015) was approved for clinical use (Sinclair and Baildon, 2006) and rapidly became a widely employed immunosuppressive drug in hepatic and cardiovascular transplantation and also in pediatric transplants (Sinclair and Baildon, 2006; Sollinger, 2004). Remarkably, MMF exhibited a potent immunosuppressive effect and less side effects than the previously employed antiproliferative immunosupressors, such as azathioprine. MMF was very effective in preventing early allograft rejection and promoting long term graft survival (Sollinger, 2004; Dalal et al., 2009). Currently, MMF represents, along with Tacrolimus, the main used drug in the prevention of allograft rejection in renal, liver and heart transplantations. In fact MMF has modified the management of immunosuppression in solid organ transplantation (Dalal et al., 2009). In 2004, another pro-drug of MPA, sodium mycophenolate (Myfortic®) (Myfortic Product information 2015), was approved.

Simultaneously to its application in organ transplantation therapy, MMF was introduced as alternative treatment for many autoimmune diseases. MMF is currently used in a wide spectrum of autoimmune diseases. Hence, MMF has been rendered very effective in the management of systemic lupus erythrematosus, primary nephrotic syndrome, and lupus nephritis (Ulinsky et al, 2005; Mak et al., 2009; Conti et al., 2014). In diabetes mellitus MMF significantly reduces the levels of human insulin antibodies (Segal et al., 2008). Moreover, MMF has been effectively used in common dermatologic conditions such as psoriasis, atopic dermatitis and pemphigus vulgaris (Rallis and Anyfantakis, 2008;

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Ricci et al., 2009). In addition, it has been reported to be effective in refractary cases of juvenile autoimmune hepatitis (Mielli-Vergani et al., 2009), in neurological autoimmune diseases as myasthenia (Benatar and Rowland, 2008), in non infectious uveitis (where has shown to be more eficacious and less toxic than other immunosuppresive drugs as second step therapy (Salzmann and Lightman, 2000), and in different types of vasculitis (Tullus and Marks, 2009). Of note, the prevalence of autoimmune diseases is greater among the female population; thus a significative number of women in fertile age will be prescribed MMF. As a consequence there will be a potential exposure of the fetus to this drug during intrauterine life.

1.2. Pharmacokinetics and mechanism of action of MMF

MMF has almost full bioavailability by oral intake, and is almost completely hydrolyzed to the active drug, mycophenolic acid (MPA), by esterases in the stomach, small intestine, blood, liver and tissues (Sollinger, 2004; Staatz and Tett, 2007). MMF is the 2,4-morpholino-ethyl ester of MPA, it was devised as a pro-drug because the oral bioavailability of MPA is relatively low. Another pro-drug of MPA, sodium mycophenolate, is avalaible for clinicians.

MPA acts as a selective inhibitor of inosine 5'-monophosphate dehydrogenase (IMPDH) (Fig. 1). As a non-competitive inhibitor of the enzyme, MPA does not incorporate into DNA. IMPDH is the rate-limiting enzyme involved in the *de novo* synthesis of intracellular guanosine. It catalyzes the oxidation of inosine monophosphate dehydrogenase to xanthine 5'-monophosphate, an intermediate metabolite in the production of guanosine triphosphate (GTP) (Allison, 2005; Chen and Chen, 2014). MPA has potent cytostatic effects on lymphocytes proliferation, because this cells are critically dependent on *de novo* synthesis of purines, but MPA has no effect on the salvage pathway. The inhibition of DNA synthesis via depletion of intracellular guanosine results in an inhibition of the proliferative response of T and B lymphocytes to both mitogenic and allospecific stimulation and suppresses antibody formation by B lymphocytes Also, MPA is more active against IMPDH 2, the isoform that is expressed mainly in malignant, activated lymphocytes (Allison, 2005; Staatz and Tett, 2007). Moreover, decrease of GTP production prevents the expression of adhesion molecules that are responsible for recruiting monocytes and lymphocytes to sites of inflammation and graft rejection (Eugui et al., 1991). Another proposed mechanism of action of MPA is depletion of tetrahydrobiopterin (which is derived from GTP), a cofactor of inducible NO synthase (iNOS). In this way MPA inhibits the production of NO via iNOS. Activated macrophages produce NO and superoxide, which combine to generate tissue-damaging peroxynitrite (Allison, 2005).

2. Mycophenolate mofetil embryopathy

Some years after the introduction of MMF in humans, two reports of the United States National Transplantation Pregnancy Registry (NTPR) communicated for the first time the observation of fetal malformations after in utero exposure to MMF in two pregnant recipients of kidney transplant (Pérgola et al., 2001; Armenti et al., 2004). The malformations observed were short fingers and toenails and an aberrant vessel between trachea and esophagus in one case, and microtia and cleft lip and palate in the other. Further single clinical observations were reported associating in utero exposure to MMF with fetal malformations. Interestingly, these reports showed a relatively constant pattern in MMF related birth defects, consisting basically of microtia with aural atresia (hypoplasia/atresia of auditory canal); cleft lip/palate, and other associated malformations (Le Ray et al., 2004; Sifontis et al., 2006; Tjeertes et al., 2007; El Seebaly et al., 2007).

In 2008, we reported the case of a baby, born to a kidney-transplanted recipient woman, with craniofacial malformations very similar to the previously reported (Perez-Aytes et al., 2008). Based on the principle of a “rare defect” associated with a “rare environmental exposure” (Shepard, 1994; Carey et al., 2009), we proposed the existence of a specific MMF embryopathy (Perez-Aytes et al., 2008). In the case of MMF, the occurrence of a rare malformative pattern associated with an infrequent prenatal drug exposure, suggested a specific embryopathy because of the rarity of both events occurring together (Table 1). This report prompted us to send a clinical alert comment, collecting three additional reports, stressing the cautious use of MMF in pregnant women (Vento et al., 2008). All the patients reported were under combined therapy with MMF and other immunosupressors, such as cyclosporine, tacrolimus, azathioprine, or prednisolone. Even though low birth weight had been related with in utero exposure to cyclosporine and tacrolimus, no specific malformative effects on the fetus have been described with the use of all these drugs during pregnancy (Østensen et al., 2006; Fuchs and Coustan, 2007; Perez-Aytes et al., 2010).

In 2009, Anderka et al. (2009) reported an additional patient with MMF-related birth defects, reviewed the literature, and found 14 single clinical observations reported until then. From these 14 patients, 12 presented with microtia and/or aural atresia, and within these 12 patients, 6 had cleft lip and/or palate. Other congenital defects were ocular defects in 6 (microphthalmia; iris coloboma; chorioretinal coloboma), congenital vascular heart defects in 4, hypoplastic fingers and toenails in 3, micrognathia in 2, esophageal atresia in 1, and 1 congenital diaphragmatic hernia. After the Anderka et al. report, at least 11 additional patients with major malformations after exposure to MMF have been reported as single case clinical observation, totaling 25 cases of MMF-related

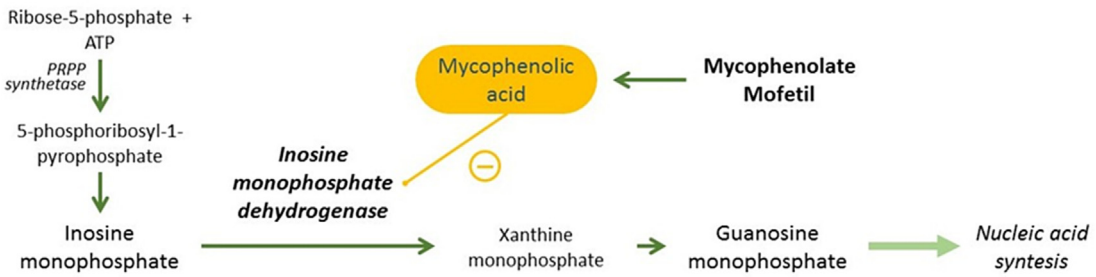

Fig. 1. Mycofenolic acid, the active metabolite of Mycophenolate mofetil, acts as a potent, non competitive inhibitor, of inosine monophosphate dehydrogenase with selective action of the novo synthesis of purines necessaries for activation and proliferation of lymphocytes.

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