CLINICAL REPORT

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Reviewing the Evidence for Mycophenolate Mofetil as a New Teratogen: Case Report and Review of the Literature

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Mycophenolate mofetil (MMF) (CellCept®) is an immunosuppressant drug that is teratogenic in rats and rabbits. Reports of malformations in 13 offspring of women exposed to MMF in pregnancy raise concern that MMF is also a human teratogen. We report an additional child with malformations following prenatal exposure to MMF and review the other 13 reports. We identified a Cambodian male born at 31 weeks' gestation to a mother who had been treated for lupus nephritis with MMF from before conception to 12 weeks' gestational age. He had bilateral moderate-to-severe microtia, external auditory canal atresia, bilateral conductive hearing loss, mild microcephaly, and apparently normal development. Among the 14 MMF-exposed offspring now reported, the underlying maternal conditions were kidney transplantation (7), lupus nephritis (4), liver transplantation (1), heart transplantation (1), and recurrent erythema multiforme (1). All were exposed in early pregnancy. The most distinctive malformation was moderate-to-severe microtia or anotia (12), with external auditory canal atresia in 9. Other common craniofacial malformations and minor anomalies included orofacial clefts (7), hypertelorism (3), coloboma (3), and micrognathia (3). Six had cardiovascular malformations, of which three were either conotruncal or aortic arch defects. MMF dose, reported in 12 patients, was <1 g/day in 4 and 1 g or more/day in 8; no correlation between dose and phenotype severity was apparent. While case reports have limited value in identifying human teratogens, the unusual distribution of malformations among the 14 reported exposed offspring identifies a phenotype suggesting that MMF is likely a human teratogen.

Key words: CellCept®; cleft lip and palate; coloboma; malformation; microtia; mycophenolate mofetil; teratogenesis

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INTRODUCTION

Mycophenolate mofetil (MMF) is a relatively new immunosuppressant used in transplant patients to prevent rejection and in autoimmune conditions to reduce inflammation. MMF, a prodrug of mycophenolic acid, is marketed under the brand name CellCept® (Roche Laboratories, 2007) and was approved by the U.S. Food and Drug Administration (FDA) in 1995. MMF blocks purine

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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biosynthesis through inhibition of the enzyme inosine monophosphate dehydrogenase, thus reducing DNA synthesis and inhibiting T- and B-lymphocyte proliferation. MMF also induces apoptosis of T-lymphocytes and reduces synthesis of antibodies [Allison and Eugui, 2000].

The use of MMF in transplant patients has increased over time [Kaufman et al., 2004; Hesselink and van Gelder, 2005]. In the U.S., MMF is now used by nearly 80% of kidney transplant patients and about half of liver transplant patients [Kaufman et al., 2004; Meier-Kriesche et al., 2006]. Off-label use for autoimmune diseases, such as systemic lupus erythematosus (SLE) and dermatologic conditions, such as psoriasis [Gregoor et al., 2000; Callen, 2001; Frieling and Luger, 2002; Liu and Mackool, 2003], may lead to even wider use. Because pregnancies are occurring more frequently in transplant patients [McKay and Josephson, 2006], and autoimmune conditions often occur in women in their childbearing years, it is critical to determine the safety of MMF use during pregnancy.

Premarketing animal studies documented that MMF is teratogenic in both rats and rabbits [Tendron et al., 2002; Roche Package Insert, 2007], and the package insert initially included an FDA pregnancy category rating of C (human data lacking, animal studies positive or not done; interpreted to mean that the risk of fetal harm cannot be ruled out). Subsequent data from a transplantation registry and case reports in offspring of women who took MMF in pregnancy have increased concern that MMF may also be teratogenic in humans [Pérgola et al., 2001; Armenti et al., 2004; LeRay et al., 2004; Källén et al., 2005; Sifontis et al., 2006; Perez-Aytes et al., 2007; Sebaaly et al., 2007; Tjeertes et al., 2007; Ang et al., 2008; Schoner et al., 2008; Velinov and Zellers, 2008; Vila et al., 2008]. These data led the FDA to recently change the pregnancy category to D (human data show risk; benefits may be viewed as acceptable in some instances) (http://www.fda.gov/medwatch/SAFETY/2007/Myfortic_DHCP_Letter.pdf).

We describe another patient with malformations who was exposed in utero to MMF, and review the evidence to date regarding the possible human teratogenicity of MMF.

CLINICAL REPORT

This Cambodian male was born by vaginal delivery to a 19-year-old primigravida mother at 31 weeks' gestation. The pregnancy was complicated by lupus nephritis, and the mother was treated with MMF (1 g bid) for the first 11–12 weeks of gestation and with prednisone throughout the pregnancy. Hydroxychloroquine and lisinopril were discontinued in early pregnancy. Delivery was induced at 31 weeks' gestation because of intrauterine growth restriction. The birth weight was 980 g (less than 10th percentile), length was 37 cm (10th percentile), and head circumference was 26.5 cm (less than 10th percentile). He was noted to have bilateral microtia, with a slightly small right pinna and preauricular pit. The left pinna was malformed, elongated, about one-half of normal width and had no external auditory canal. There was a sacral dimple with a small tuft of hair, but spinal ultrasonographic examination was normal. His foreskin was tethered, and bilateral inguinal herniae were surgically repaired at age 7 weeks. Renal ultrasound was normal. Audiology studies showed a bilateral moderate-to-severe conductive hearing loss; he was fitted with bone conduction hearing aids and enrolled in an early intervention program (see Fig. 1). Chromosome analysis was normal, but oligonucleotide microarray analysis showed a 12p13.2 duplication, which was inherited from a phenotypically normal father and presumed to be a benign copy number variant.

Psychomotor development appears to be age appropriate by parental report and informal observation: He walked at the age of 1 year, and when last seen at the age of 3 years and 7 months, he was socially interactive, spoke in 3- and 4-word sentences, knew several signs, attended a regular (not special education) preschool, counted to 10, and recited most of the alphabet. Growth charts indicated catch-up growth into the low normal range for height by 21 months, which subsequently increased to the 50th percentile; his weight reached the 25th percentile by the age of 3 years. However, his head circumference had fallen to less than the 5th percentile. Cerebral imaging is planned for the future.

DISCUSSION AND LITERATURE REVIEW

This additional report of a prenatally exposed infant adds to the 13 other reports currently available (summarized in Table I) [Pérgola et al., 2001; Armenti et al., 2004; LeRay et al., 2004; Källén et al., 2005; Sifontis et al., 2006; Perez-Aytes et al., 2007; Sebaaly et al., 2007; Tjeertes et al., 2007; Ang et al., 2008; Schoner et al., 2008; Velinov and Zellers, 2008; Vila et al., 2008]. Of these 14 reports, four were ascertained through the National Transplantation Pregnancy Registry and the remainder were case reports. Three of the reported cases were elective pregnancy terminations and 11 were liveborn infants; among the latter, 6 of 9 with known gestational age had been delivered preterm (<37 weeks' gestation).

Craniofacial malformations were reported in 12 of the 14 offspring; among the most common were moderate-to-severe microtia or anotia (12 infants), and among those, 9 had atresia of the external auditory canal. The malformed pinnae depicted in selected reports were elongated or cupped (reprinted with permission from publisher in Fig. 1). Orofacial clefts (affecting seven infants) included cleft lip and palate (four), cleft palate (two), and bilateral oblique facial cleft (one). Hypertelorism was reported in three patients and is also suspected from our review of the photograph of the patient reported in Ang et al. [2008, Fig. 1B]. Micrognathia was reported in three patients. Ocular malformations were noted in five infants and included colobomas in three (chorioretinal coloboma in one; eyelid, iris, and retinal coloboma with severe microphthalmia and complex retinal dysplasia in one; and iris and chorioretinal coloboma in one). One additional infant had an unspecified "iris anomaly" and another had "left eye microftalmia" [*sic*]. Cardiovascular malformations (CVMs) were present in six infants and three of those had conotruncal and/or aortic arch defects and one was described as an unspecified "complex" defect. Three patients had a kidney defect (one each with renal agenesis, kidney "asymmetry" (possibly hypoplasia), and pelvic kidney). Two patients each had esophageal atresia and agenesis of the corpus callosum. Digital anomalies in four patients involved a reduction in size, such as hypoplastic nails in two infants, and brachydactyly and digitalized thumbs in one each.

Psychomotor outcome data are sparse for the 10 evaluable infants [present patient; Pérgola et al., 2001; Armenti et al.,

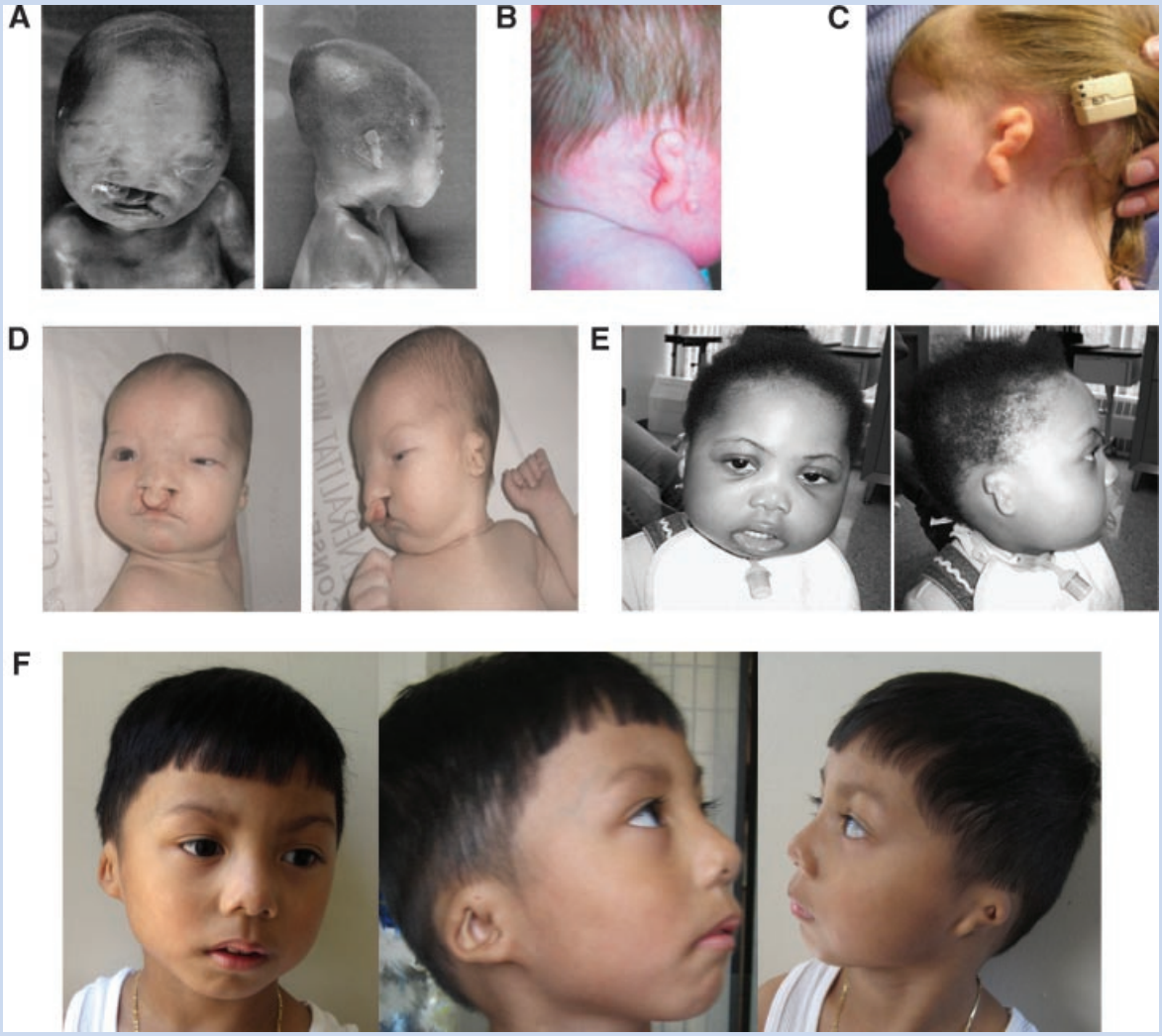

FIG. 1. Comparison of the facial appearance of patients with MMF embryopathy (five selected from literature, one new). A: Figures 1 and 2 [LeRay et al., 2004]. B: Figure 1 [Tjeertes et al., 2007]. C: Figure 1a [Ang et al., 2008]. D: Figure 1a,b [Perez-Aytes et al., 2007]. E: Figures 2 and 1 [Velinov and Zellers, 2008]. F: Present patient: a, b, and c. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

2004; Källén et al., 2005; Sifontis et al., 2006; Perez-Aytes et al., 2007; Tjeertes et al., 2007; Ang et al., 2008; Velinov and Zellers, 2008; Vila et al., 2008]. Agenesis of the corpus callosum has been noted in two patients and the present patient has microcephaly, but appears to be developing normally at $3^1/_2$ years.

Comparison With Other Syndromes

The constellation of craniofacial malformations and minor anomalies present in the patients exposed to MMF has some overlap with a few familiar syndromes, but the disorders should not be confused. These include CHARGE syndrome [Sanlaville and Verloes, 2007], hemifacial microsomia [Vento et al., 1991], also known as oculoauriculovertebral dysplasia or facioauriculoverterbral spectrum, and retinoic acid embryopathy [Lammer et al. 1985; Lynberg et al., 1990; Lammer, 1991]. The rare hypertelorism–microtia–clefting syndrome (HMC) (Bixler syndrome) [Verloes, 1994; Amiel et al., 2001] should also be included in this differential diagnosis. Schoner et al. [2008] suggested that the severe oblique facial clefts and digitalized thumbs (approximating a triphalangeal thumb) in the terminated fetus resembled a severe form of Nager syndrome [McDonald and Gorksi, 1993; Opitz et al., 1993], which would be an atypical presentation.

Assessing Teratogenicity Based on Established Principles

Several factors have been suggested as helpful in assessing a potential teratogen [Table I in Brent, 1993; Shepard, 1994]; these include (1) epidemiologic studies demonstrating an association between an exposure and adverse birth outcome, (2) evidence of teratogenicity in experimental animals, (3) temporal plausibility of the exposure/

TABLE I. Clinical Features in Patients Exposed to Mycophenolate Mofetil (14 Total, 13 Literature, 1 New Patient)

Pt #	Pt source	Maternal factors and condition(s)	MMF	Other immunosuppressants	Other medication	Neonatal summary	Microtia hearing loss	Cleft lip/ palate	Other facial	Other
1	Present pt	Cambodian 19-year-old mother. SLE glomerulonephritis without organ transplant	1 g twice a day: for 1 month. Off briefly for 2 months, but restarted on the day before LMP. Discontinued at 12 weeks	Prednisone (dose NS)	Lisinopril, hydroxychloroquine, oral iron, prenatal vitamins, calcium, vitamin D, acetaminophen	Male, 31 weeks, birth weight—980 g. Normal development at 4 years	Bilateral, severe. Preauricular pit. EAC left. Moderate conductive deafness left, mild on right	Not present	Not present	Tethered foreskin. Left hydrocele. Bilateral inguinal herniae. Sacral dimple. Postnatal blood karyotype—46,XY. aCGH dup12p pat.[a]
2	Pérgola et al. [2001] [pt 1 of Sifontis et al., 2006]	33-year-old, G3P2 gestational DM. ESRD "unclear etiology," second kidney transplant	Transplanted at 6–7 weeks gest. 1 g bid until 26 weeks; 500 mg bid until delivery	Tacrolimus (7 mg/day), prednisone (25 mg/day)	Nifedipine, trimethoprim/ sulfamethoxazole, nystatin solution, acyclovir, famotidine, oral iron, prenatal vitamins	Female, 34 weeks, birth weight—2,250 g (75%ile). Birth HC 29.5 cm (10–25th %ile). Reportedly, developing well at 6 years	Not present	Not present	Not present	Hypoplastic finger and toenails. Bilaterally shortened fifth finger. "Aberrant blood vessel between trachea and esophagus"[b]
3	Armenti et al. [2004] [pt 2 of Sifontis et al., 2006]	NS. Kidney transplant	500 mg bid until 24 weeks	Tacrolimus (dose NS), prednisone (dose NS), sirolimus (from 24 weeks to delivery), anti-thymocyte globulin (added at 24 weeks)	Labetolol, omeprazole, clindamycin, ganciclovir, erythropoietin, aztreonam	NS, 31 weeks, birth weight—1,531 g. Reportedly, doing well at 4 years	Yes, conductive deafness	Yes		
4	LeRay et al. [2004]	27-year-old G1 White. ESRD "renal atrophy," kidney transplant	500 mg/day until 13 weeks	Tacrolimus (9 mg/day), prednisone (15 mg/day), azathioprine (50 mg/day from 13 weeks to delivery)		Male, 22 weeks, "normal" growth, TOP	Bilateral, severe, EAC atresia	Yes	Micrognathia, hypertelorism	Left pelvic ectopic kidney, agenesis corpus callosum
5	Källén et al. [2005]	22 years old. Liver transplant	"Early pregnancy," Dose NS	Tacrolimus (dose NS), prednisone (dose NS)	Ursodeoxycholic acid		Not present	Not present	Iris anomaly	Esophageal atresia and complex cardiac defect, NOS
6	Sifontis et al. [2006] (pt 3)	NS. kidney transplant	250 mg bid throughout pregnancy	Tacrolimus (dose NS). prednisone (dose NS)	amlodipine, metoprolol, furosemide, prenatal vitamins, erythropoietin, aspirin, acyclovir	NS, 35 weeks, birth weight—2,155 g, died on day 1	Yes	Yes		Congenital diaphragmatic hernia. Congenital heart defect, NOS. "Fryn's syndrome" suggested[c]
7	Sifontis et al. [2006] (pt 4)	NS. Kidney transplant	1 g bid until 15 weeks	Tacrolimus (dose NS), prednisone (dose NS)	Acyclovir	NS, 39 weeks, 2,886 g	Yes			
8	Tjeertes et al. [2007]	36 years old, White, G5P1Sab3. VUR, kidney transplant	Throughout pregnancy, dose NS	Tacrolimus (dose NS), prednisolone (throughout pregnancy)	Olanzapine, nitrazepam, diazepam (month 4), haloperidol (month 4), darbepoetin alfa (last months of pregnancy), methyldopa (last months of pregnancy)	Male, 35 weeks, 2,330 g	Yes, EAC right ear			Hydrops fetalis
9	Sebaaly et al. [2007]	21 years old. SLE nephritis without transplant	1 g bid until 25 weeks	Prednisone (dose NS), hydroxychloroquine	Perindopril	25 weeks, TOP	Anotia, bilateral EAC atresia	No		Polydactyly, hypoplastic nails, VSD, "anterior aorta,"[d] kidney "asymmetry."[e] Normal karyotype
10	Perez-Aytes et al. [2007]	Spanish, 25-year-old mother. Late diagnosed VUR, kidney transplant	500 mg/day until 10 weeks	Tacrolimus (12 mg/day)		Female, 41 weeks, birth weight—3,050 g. Normal development at 9 months	Bilateral, severe EAC atresia. Severe conductive deafness	Yes	Micrognathia, hypertelorism, bilateral chorio-retinal coloboma	Amnio 46,XX, normal brain CT

(*Continued*)

TABLE I. (*Continued*)

Pt #	Pt source	Maternal factors and condition(s)	MMF	Other immunosuppressants	Other medication	Neonatal summary	Microtia hearing loss	Cleft lip/ palate	Other facial	Other
11	Velinov and Zellers [2008]	Black, SLE, nephritis without transplant	500 mg bid, first 8 weeks of pregnancy	Adalimumab (40 mg every other week)		Female, 32 weeks, birth weight—4,442 g. Global development delay, mild motor, significant speech	Bilateral severe EAC atresia	Cleft palate only	Arched brows, hypertelorism, epicanthal folds, everted lower lip. Severe tracheo-malacia, micrognathia	Brachydactyly, 46,XX 22q11 microdeletion: negative
12	Schoner et al. [2008]	White. SLE without transplant	MMF, 250–750 bid prior to conception to week 8	Cyclophosphamide (800 mg, schedule NS), azathioprine (50 mg bid throughout)		Female, TOP 17 weeks, multiple severe anomalies. Autopsy performed	Bilateral severe (virtual anotia), EAC atresia	Bilateral facial cleft and CL/P	Eyelid, iris, retinal coloboma. Severe microphthalmia, lens dislocation, severe mandibular hypoplasia, absent maxilla and orbits, cataracts	Agenesis corpus callosum, mild HC. Bilateral digitalized thumbs. Truncus arteriosus, ARSCA. Esophageal atresia. Left renal agenesis, streak ovary. Hemivertebrae, rib defect. Single umbilical artery. "Possible Nager phenocopy" CVS 46,XX, scoliosis
13	Ang et al. [2008]	White. Recurrent erythema multiforme	MMF 500 mg bid for 4 days during the 5th week of pregnancy	None	None	Female, livebirth, 40 weeks, birth weight—2,900 g	Bilateral microtia, EAC atresia, bilateral conductive hearing loss	None	Right iris and chorioretinal coloboma in the right eye Hypertelorism possible[f]	Normal cognitive development, normal echocardiogram, renal sonogram, vertebral radiographs, normal MRI of cerebrum and structures of inner ear
14	Vila et al. [2008]	35 years old. Heart transplant for severe congestive heart failure. Seizure disorder	MMF 500 mg tid changed to 250 mg bid at 5 weeks of pregnancy	Tacrolimus (3 mg bid), prednisone (5 mg/day)	Pravastatin (40 mg/day), diltiazem (60 mg tid), carbamazepine	Livebirth	EAC and middle ear atresia bilaterally, "bad formation of auricular pavilion"	Palatine gap	"Left eye microftalmia" [sic]	Umbilical hernia "Light pulmonary valve stenosis"

Table adapted from Perez-Aytes et al. [2007].
ARSCA, aberrant right subclavian artery; CL/P, cleft lip and palate; CPO, cleft palate only; CVS, chorionic villus sampling; DM, diabetes mellitus; EAC, external auditory canal; ESRD, end-stage renal disease; HC, hydrocephaly; MMF, mycophenolate mofetil; NS, not stated, or not specified; Pt, patient; SLE, systemic lupus erythematosus; TOP, termination of pregnancy; VSD, ventricular septal defect; VUR, vesico-ureteral reflux.
[a]aCGH, chromosome microarray analysis showed duplication at 12p which was paternally inherited.
[b]Suspect that this description implies possible aberrant subclavian artery, or some other arch anomaly.
[c]Sifontis et al. [2006] do not specify how this diagnosis was made stating that "medical records suggest a possible association of these observed structural malformations with Fryn's (sic) syndrome."
[d]VSD with "anterior aorta" may be a possible malalignment-type VSD.
[e]"Asymmetry" of kidneys may be possible renal hypoplasia.
[f]Appears to have hypertelorism based on review of clinical photograph.

disease relationship, (4) evidence of a dose–response relationship between exposure and outcome, and (5) a biologically plausible mechanism by which the agent could act to produce the birth defects observed.

A recent editorial addressing MMF exposure highlights the fact that "astute" observations can be helpful in inferring potential consequences of an exposure during pregnancy [Carey, 2008]. Reports of individual cases or case series recognized by attentive clinicians may provide the initial indication that adverse outcomes might be occurring, particularly when a rare exposure is associated with a rare defect or a distinctive pattern of defects [Carey, 2002]. However, case reports alone make it difficult to ascribe teratogenicity because they are subject to biased reporting and lack a denominator, limiting the ability to estimate the frequency of an outcome following the exposure. Formal epidemiologic studies related to MMF in pregnancy have not been published, probably due to the fact that use of the drug, while increasing, has not been sufficiently high to make such studies feasible. Such studies would provide magnitude to the risk estimates, not possible with case reports.

Two aspects of the currently available human data contribute support to the view that MMF may be a human teratogen. First, as detailed below, review of the 14 reported cases suggests a specific pattern of malformations, although reporting bias is always a possible explanation. Second, it is noteworthy that 4 of the 14 exposed/malformed patients were observed as part of the National Transplantation Pregnancy Registry, which included 23 women with 32 pregnancies exposed to MMF [Armenti et al., 2005]; 14 of these pregnancies resulted in spontaneous abortions. Among the 18 pregnancies that resulted in livebirths, 4 (22%) were associated with malformations in the offspring. However, reports to the pregnancy registry were voluntary and pregnancies with abnormalities may be more likely to be reported to the registry, resulting in an overestimate of the frequency of defects among exposed offspring [Kennedy et al., 2004].

Studies in rats and rabbits both demonstrate an increased risk for birth defects among exposed animals. In rats, the MMF-associated malformations were seen at doses lower than or roughly equivalent to human doses and included anophthalmia, agnathia, and hydrocephaly. In rabbits, ectopia cordis, ectopic kidneys, diaphragmatic hernia, and umbilical hernia were seen [Tendron et al., 2002; Sifontis et al., 2006; Schoner et al., 2008]. Birth defects observed in both animal studies and case reports in humans included diaphragmatic hernia, ocular, heart, and kidney defects. The most common defect observed in humans, microtia, was not seen in the animal studies. While animal models often do not predict the human response [Carney et al., 2004], the concordance for many MMF-related defects between animal studies and human data is noteworthy.

With respect to temporal plausibility, in all infants born to mothers exposed to MMF, the timing of exposure was known and included the first trimester of pregnancy—timing consistent with the period of organogenesis for the observed malformations. In the infant reported by Ang et al. [2008] with bilateral microtia, absence of the external auditory canals, and right iris and chorioretinal coloboma, a narrow window of exposure was reported (4 days in the 5th week of pregnancy [7th week after LMP]), but this exposure timing is consistent with the malformations observed (microtia and coloboma) [Moller, 2005]. Among the 14 cases reported, there was no apparent relationship between MMF dose and phenotype severity (see Table I).

As is the case for most known teratogens, it is difficult to infer a biologic mechanism by which MMF might be teratogenic. It is known that MMF crosses the placenta [Tendron et al., 2002] and that this prodrug of mycophenolic acid is a reversible inhibitor of the enzyme inosine monophosphate dehydrogenase, which is necessary for de novo purine synthesis. Although most cell types can generate purines through either de novo or salvage pathways, lymphocytes are dependent on the de novo pathway; thus, MMF's major therapeutic mechanism of action is to decrease DNA production, resulting in a cytostatic effect on B- and T-lymphocytes. It is unknown whether MMF could have a similar effect on rapidly growing cells of the embryo, and how its actions might specifically result in the malformations observed is unclear.

Limitations

Although our review of the evidence supports the premise that MMF is a teratogen, several challenges exist. All of the exposed mothers had serious underlying conditions and these conditions could themselves increase the risk for birth defects [Källén et al., 2005; Phadungkiawattana et al., 2007]. However, observation of a pattern of malformations in the offspring of women receiving MMF for different underlying conditions (e.g., post-transplant, lupus nephritis, erythema multiforme) adds weight to the findings that it is the MMF, and not the underlying disease, that may be teratogenic.

Another challenge is that all but one (patient #13, Table I) of the MMF-exposed mothers had received additional immunosuppressive medications. Eight mothers received prednisone and tacrolimus, another tacrolimus alone, and another two prednisone alone. Of note, however, three patients (patients #11, #12, and #13, Table I), who were not exposed to either prednisone or tacrolimus, had significant ear defects. Azathioprine was taken by the mothers of two reported patients—one throughout pregnancy and one after the first trimester only. Azathioprine has been shown to cause skeletal and visceral anomalies in mice and rabbits. One patient exposed to both MMF and azathioprine had skeletal malformations, in addition to those defects consistent with MMF exposure (patient #12, Table I) and possibly was adversely affected by both exposures to both medications. None of the other medications to which women were exposed is known to be a teratogen, although information on the safety of these medications during pregnancy is severely limited [Lo and Friedman, 2002].

A recent commentary argued that based on rarity of exposure to MMF, consistency in the pattern of malformations observed, and biological plausibility, a causal association between MMF and the malformations is likely [Vento et al., 2008]. Despite the support provided by the registry data and the distribution of defects seen in the reported cases, definitive evidence that MMF is a human teratogen would best come from formally conducted epidemiologic studies that could provide information on both the frequency and nature of malformations among exposed infants relative to appropriately selected unexposed infants.

CONCLUSION

Caution is needed in interpreting clinical case reports that associate drug exposure with isolated malformations. Based on this case report and the available literature, including the experience of a transplantation pregnancy registry, we believe the pattern of malformations and minor facial anomalies is sufficiently consistent to support MMF as a likely teratogen. In a fetus or infant who has been exposed to MMF, detection of this pattern malformations and minor facial anomalies (bilateral microtia, orofacial cleft, coloboma, hypertelorism, micrognathia, conotruncal CHD, agenesis of the corpus callosum, esophageal atresia, digital hypoplasia) should prompt consideration of the embryopathy.

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