Mycophenolate mofetil

Emerging as a potential human teratogen

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ABSTRACT

QUESTION One of my female patients conceived 2 years after renal transplant while using mycophenolate mofetil. She only realized she was pregnant at 14 weeks of gestation. How should I advise her?

ANSWER Several recent case series show increased malformation rates with mycophenolate mofetil. Specifically, the repeated occurrence of phenotypic presentations of ear malformations, cleft lip and palate, and other malformations suggest that this is not by chance alone.

RÉSUMÉ

QUESTION Une de mes patientes est devenue enceinte 2 ans après une greffe de rein, alors qu'elle prenait du mycophénolate mofétil. Elle ne s'est rendu compte de sa grossesse qu'après 14 semaines de gestation. Quels conseils devrais-je lui donner?

RÉPONSE Selon plusieurs séries de cas récents, les taux de malformations sont plus élevés avec le mycophénolate mofétil. Plus précisément, la survenance répétée de présentations phénotypiques de malformations de l'oreille, de bec-de-lièvre, de fentes palatines et d'autres malformations porte à conclure que ce n'est pas le seul fait du hasard.

Pregnant women cannot discontinue their transplant medications, as this can result in potential organ rejection. This is one situation in which continuous pharmacotherapy in pregnancy is undebatable and, hence, careful analysis of fetal safety is critical.

The first-generation antirejection drug cyclosporine, combined with corticosteroids and azathioprine, revolutionized the survival of organ transplant patients and has led the clinical scene for more than 2 decades. However, chronic exposure to cyclosporine is often associated with severe adverse effects, most notably renal failure.

Among the novel antirejection medications that are emerging, mycophenolate mofetil has had substantial success, partially because of its lack of adverse renal effects. Mycophenolate mofetil is an ester prodrug of mycophenolic acid, a reversible inhibitor of inosine monophosphate dehydrogenase, blocking de novo purine synthesis in T- and B-lymphocytes.[1]

Animal studies

Similar to all new drugs, premarketing studies of this medication included animal teratology studies. Studies in pregnant rats and rabbits suggested increased risks of congenital malformations, including anophthalmia, agnathia, hydrocephaly, and diaphragmatic hernia, at schedules not exceeding surface area–normalized human doses.[2-5] Although, oftentimes teratogenic results in animals do not translate to human teratology, even at equivalent human doses, with half of all pregnancies unplanned, many women conceive while using medication. So, despite the mycophenolate mofetil manufacturer's strong recommendation for effective contraception before the start of mycophenolic therapy, there is an increasing number of reported fetal exposures being registered.

Teratogenic effect

It is often difficult to interpret single case reports of malformations, as these reports do not easily prove causation. For example, if a drug commonly used by many pregnant women is reported to be associated with single case reports of ventricular septal defects in neonates, the cases would most likely be dismissed; it is unlikely that such cases would show causation because one would expect some of those neonates to have common spontaneous malformations.

The situation is different, however, when a drug that is not commonly used by pregnant women causes rare malformations. In these circumstances, even a small number of cases strongly suggest causation. This has been the case with several drugs, such as isotretinoin and warfarin.

With respect to mycophenolate mofetil, case reports and case series in the past few years have repeatedly described babies with phenotypic appearance, including microtia (small ears), cleft lip and palate, micrognathia

Malformations associated with mycophenolate mofetil

Reported malformations of babies after first-trimester exposure to mycophenolate mofetil include the following:

- microtia,
- cleft lip and palate,
- hypoplastic fingers and toenails,
- diaphragmatic hernia,
- congenital heart defects, and
- micrognathia.

congenital diaphragmatic hernia, congenital heart defects, and hypoplastic fingers and toenails, after first-trimester exposure.[6-9] If these malformations occurred by chance, one would not expect phenotypic clustering of such defects but rather a distribution similar to malformation incidence in the general population. Because at the present time mycophenolate mofetil is rarely used in pregnant women and some of the described malformations (eg, ear malformations) are very rare, such clustering of case reports might show causation. Although there is a strong suggestion of a teratogenic effect, a prospective collection of cases is critical to be able to estimate the magnitude of risk, as such estimates are critical in counseling.

Conclusion

In a post-transplant woman who is using mycophenolate mofetil and considering pregnancy, the option to switch to cyclosporine, even for a short period of time, has to be considered, as cyclosporine has not been associated with either morphological or neurodevelopmental teratology in humans.[10] Such a decision must be made by transplant experts, optimally as part of a multidisciplinary team, which should include the woman's personal physician, a high-risk perinatologist, and a geneticist, among others. More studies are urgently needed to calculate the absolute teratogenic risk of this drug.

Competing interests

None declared

References

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MOTHERISK

Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in Toronto, Ont. **Dr Koren** is Director of the Motherisk Program. He is supported by the Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation. He holds the Ivey Chair in Molecular Toxicology at the University of Western Ontario in London.

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