

Correspondence

Changing of the Guards: EMA Warning on Paternal Use of Mycophenolate Mofetil: An Unnecessary and Insufficiently Substantiated Precaution

On October 23, 2015, the European Medicines Agency (EMA) issued a press release and subsequently recommended a change to the Summary of Product Characteristics (SmPC) for mycophenolate mofetil (MMF) (EMA, 2015a,b). This specifically addressed pregnancy related issues and the wording in SmPC sections 4.4 (Special warnings and precautions for use) and 4.6 (Pregnancy and lactation) (EMA, 2015b). A *Direct Healthcare Professional Communication* from the manufacturer followed the EMA press release (Roche, 2015). The new warnings and precautions now for the first time included a specific statement on paternal exposure before conception, stating that: “*Sexually active men are recommended to use condoms during treatment and for at least 90 days after cessation of treatment*” (EMA, 2015b). The rationale or supporting evidence behind these recommendations is not presented. The FDA SmPC does not hold a similar warning (FDA, 2016).

These are very strong measures called upon by a regulatory authority that in effect mean that renal transplant recipients receiving MMF de facto cannot (or at the very least are strongly advised not to) father a child. Complying with EMA precautions, planned fatherhood would require substituting MMF with a different immunosuppressant drug such as azathioprine; this would not be without risk of organ rejection or serious adverse reactions. We believe these precautionary measures are unsubstantiated by any meaningful level of evidence, and we believe they introduce unnecessary concerns to clinicians and organ transplant recipients planning fatherhood as well as parents-to-be who conceived during paternal use of MMF. In our respective Drug and Teratology Information Services across three European countries, we have received many calls from confused clinicians and worried male renal transplant recipients planning fatherhood. These include questions about termination of pregnancy in case of paternal exposure.

MMF is a well-documented human teratogen following first trimester in utero exposure, and appropriate precautions are suggested in the SmPC (Anderka et al., 2009; Hoeltzenbein et al., 2012; EMA, 2015b). The amount of human data relating to paternal exposure is moderate but quite reassuring, and does not suggest a level of risk that justifies the EMA warnings and precautions. The United States National Transplantation

Pregnancy Registry (NTPR) identified 205 pregnancies fathered by 152 transplant recipients who received MMF at the estimated time of conception (Jones et al., 2013). Among 194 live births, the rates of malformations, miscarriages and prematurity were 3.1% (no specific pattern), 6.8% and 11%, respectively. All of these observations are well with the expected range. The NTPR has since collected 70 additional cases with no signs of adverse fetal outcome (*personal communication*, Michael J. Moritz, NTPR, December 2015). A Norwegian study, reported 2463 male organ transplant recipients who fathered 4614 children before transplantation and 474 children after transplantation (Morken et al., 2015). Following organ transplantation, no increased risk was found for any adverse pregnancy outcomes compared with outcomes before organ transplantation or to general population estimates. While specific drug exposure data including MMF is not available from the paper, the majority of the transplant recipients will have received MMF.

In vitro and animal data from the SmPC does not suggest a reproductive toxicity profile of MMF that justifies the current precautions (EMA, 2015b). Two genotoxicity assays (in vitro mouse lymphoma assay and in vivo mouse bone marrow micronucleus test) showed a weak potential of MMF to cause chromosomal aberrations at extremely high doses (300 mg/kg/day) in vivo in mice. Other in vitro tests for detection of gene mutation did not demonstrate genotoxic activity. MMF had no effect on fertility of male rats at oral doses up to 20 mg/kg/day. The systemic exposure at this dose represents 2 to 3 times the clinical exposure at the recommended clinical dose of 2 gram/day in renal transplant recipients (EMA, 2006; EMA, 2015b). There are no specific data on transfer of MMF in seminal fluid, but such transfer is unlikely to be of clinical relevance (Scialli et al., 2015).

We conclude that the available data do not justify the new precautions to male transplant recipients issued by EMA, which are inconsistent with FDA recommendations. We believe that EMA must reconsider this particular change to the SmPC. We believe that EMA should present evidence that contradicts the available human data presented above rather than relying on speculative theoretical concerns of potential chromosomal damage or transfer of infinitesimal amounts of MMF through seminal fluid.

In any case, it should be recommended that such suggested risk should be discussed on an individual level with a

specifically qualified health-care professional, for example, a Teratology Information Service. As the SmPC wording stands, the suggested precautions subject organ transplant recipients receiving MMF and contemplating fatherhood to an unnecessary loss.

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