Transplantation Publish Ahead of Print
DOI: 10.1097/TP.0000000000001509

Mycophenolate Acid and Balancing the Risk for Male Allograft Recipients

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Both authors declare no conflict of interest.

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Abbreviations

C_{max} ; Maximal concentration

EMA ; European Medicines Agency

MMF ; mycophenolate mofetil

MPA ; mycophenolic acid

We want to thank Kuypers and co-authors for addressing and commenting the updated manufacturer and European Medicines Agency (EMA) recommendations on the use of mycophenolate acid in renal transplant recipients (1,2). It is common practice in the transplant society to change immunosuppression in female recipients who wish to become pregnant by either withdrawal of mycophenolate mofetil (MMF) or switch to azathioprine if this is deemed more appropriate for rejection prevention. It has not been common practice to switch/withdraw fertile males from MMF if they want to become fathers or if they are sexually active – as recommended by EMA. Kuypers et al could only find 1 observational study in male recipients that specifically compared the incidence of congenital abnormalities in children fathered while taking MMF to the general population (3). The results did not support the EMA recommendations. Data were updated at 26th international congress of The Transplant Society in Hong Kong, August 2016, now with 268 pregnancies /278 outcomes and the results remained the same ie comparable to and not higher than the general population (Abstract #698). Another previously published observational study focusing on pregnancies fathered by males on immunosuppression compared 4614 deliveries before with 474 deliveries after transplantation (4). The risk of preeclampsia was increased (AOR: 7.4, 95% CI:1.1-51.4) after transplantation. Importantly no increased risk was found for congenital malformations or other outcomes when compared with pregnancies before transplantation or with the general population (2511506 births) ie results not supporting the EMA recommendations. The manuscript does not specify number of pregnancies with fathers on MMF but the authors estimate approximately 140-180 (personal communication).

The EMA recommendations actually state that all "sexually active (including vasectomized) men taking MMF are recommended to use condoms".....This must indicate that a female or male sexual partner may be subject to a severe risk associated with post conception exposure to semen and/or seminal fluid from males on MMF regardless of whether pregnancy or not is a warranted outcome. This puzzles us. MMF is a small molecule. Recommended dose in organ transplant recipients is up to 1000 mg twice daily with a therapeutic mycophenolic acid (MPA) trough concentration window of 1-4 mg/L. MPA C_{max} is between 10-20 mg/L when used in the recommended dose. Normal semen volume during 1 ejaculation is 2-5 ml. Our unpublished data indicate dose linearity of MPA pharmacokinetics in the range of 100 to 1000 mg although others have shown an increased relative oral bioavailability of 250 mg as compared with 1000 mg (almost doubling) (5).

Taken the above into consideration the maximal amount of MPA in seminal fluid from 1 ejaculation would be 0.1 mg (MPA C_{max} x maximal semen volume = 0.02 mg/mL x 5 mL). We are not aware of any data suggesting that exposure of 0.1 mg MPA is toxic or teratogen Even if assuming 100% bioavailability via the vaginal route (which is unlikely) the corresponding C_{max} would be 0.0014 mg/L (5).

There is a considerable risk of recipients developing rejection with withdrawal of MMF. Rejection can lead to decreased graft and patient survival and in worst case graft loss which in heart/lung/liver recipients is equal to death. In our opinion public recommendations should be based on solid knowledge- not assumptions. We agree that more information is needed but with

the current knowledge we strongly urge the EMA recommendations to be re-written and modified.

References

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