Cyclosporine A (CsA) is a powerful immunosuppressant drug widely used in transplantation procedures and in the treatment of several autoimmune diseases. However, its therapy is associated with numerous side-effects, especially dose-related cholestasis. Mechanism(s) underlying these effects remain(s) largely unknown. Tacrolimus (FK506), a macrocycle immunosuppressant that possesses similar but more potent (10-100 folds) immunosuppressant properties compared to CsA, is considered as an alternative primary immunosuppressant to CsA in hepatic transplantation. The effect of FK506 on bile flow is at the moment unclear and little is known about its effect at the canalicular level. The aim of the present work was to perform a comparative study of CsA and FK506 on canalicular function using the well differentiated human HepaRG cell line, considering the great difference in the therapeutic doses of both drugs.

**RESULTS**

**Generation of ROS and ER stress by CsA**

**Role of cPKC, ER stress and ROS in CsA-induced cholestasis**

**CSA5**

**CPZ**

**FK**

At

**CONCLUSION**

The present findings suggest that the use of alternative drugs to CsA, such as FK506, is a promising strategy to diminish the toxic side-effects of CsA, without compromising its immunosuppressive effects, thus largely expanding its therapeutic potential.