Effect of Ozanimod (RPC1063) on Action Potential Parameters in Adult Human Purkinje Fibres

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INTRODUCTION AND PURPOSE

Ozanimod (RPC1063) is an oral, once-daily immunomodulator selectively targeting sphingosine-1-phosphate (S1P) receptor subtypes 1 (S1P1) and 5 (S1P5), that has shown therapeutic benefit in clinical trials of relapsing multiple sclerosis and ulcerative colitis. A key difference between fingolimod, a drug used to treat multiple sclerosis, and ozanimod is the former’s constitutive agonism through S1P1, S1P3, and S1P4, which may explain its improved clinical profile.

METHODS

At pacing rates of 1 and 2 Hz (mimicking normal and elevated heart rates, respectively), human PFs from female hearts were used to evaluate the effects of ozanimod and fingolimod on action potential duration (APD) at 30%, 50%, and 90% repolarization (APD30, APD50, and APD90, respectively) and on recognized pro-arrhythmia predictions (translateral (APD90–APD30), short-term variability (STV) of APD90, and incidence of early afterdepolarizations (EAD)). The positive control, flecainide, showed changes in APD, triangulation, and BE (Figure 3 and 4).

RESULTS

Ozanimod showed no significant effects on APD or pro-arrhythmia markers

Ozanimod, up to a physiological concentration of 150 nM, had no significant effects on APD and did not increase the manifestation of pro-arrhythmia markers or induce beat escape (BE); the electrical stimulus does not trigger an action potential after full repolarization (Figures 1, 2, and 5). Fingolimod showed effects on pro-arrhythmia markers

Although fingolimod, up to a physiological concentration of 500 nM, also had no significant effects on APD (Figure 6), triangulation, or EADs, it did elicit an increase in STV (APD90–APD30) (Figure 4).

Fingolimod showed effects on pro-arrhythmia markers

Fingolimod showed a dose-dependent cardiac conduction and repolarization behavior at concentrations similar to those reported in the peripheral nervous system, which may explain its higher selectivity.

The model recapitulated the clinical observations that fingolimod treatment causes dose-dependent cardiac conduction abnormalities at concentrations similar to those reported in the peripheral nervous system and which appear to be the result of S1P1 agonism.

The data agreed with the clinical observation that ozanimod has no effect on the measured conduction parameters, which appear to be the result of ozanimod’s higher selectivity.

Future work on cardiac conduction may involve the un-phosphorylated form of fingolimod and the active metabolites of ozanimod and may be extended to the effect of S1P agonists on heart rhythm, through the use of isolated and perfused human sinoatrial node.

REFERENCES


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DISCLOSURES
