Apremilast (AP), a PDE 4 inhibitor, worsens the injury induced by Isoproterenol in murine heart

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BACKGROUND
Psoriasis is an independent risk for development of myocardial infarction. Apremilast (AP) is a recently approved anti-inflammatory medication for Psoriasis. It is a Phosphodiesterase-4 (PDE-4) inhibitor and results in accumulation of intracellular cyclic AMP. While this is beneficial in suppressing inflammation, inhibition of PDE-4 could sensitize the myocardium to catecholamines, thus increasing the myocardial oxygen demand. This could prove detrimental in the setting of an ischemic attack. Hence, we studied the effect of Apremilast (AP) on Isoproterenol (ISO) induced myocardial injury.

METHODOLOGY
The study protocol was approved by the Institutional Animal Ethics Committee (IAEC no. 05/IAEC-1/2017). Male Albino Wistar Rats were divided into 7 groups- Normal, ISO, AP 2.5mg/kg + ISO, AP 5mg/kg + ISO, AP 10mg/kg + ISO, AP 20mg/kg + ISO and AP 20mg/kg per se. The treatment and per se groups received corresponding doses of AP orally, once daily for 28 days. We induced ischemic myocardial injury in the treatment and ISO groups using 2 doses of ISO 75mg/kg s.c. given 24 hours apart. On the 29th day, the animals were sacrificed after measurement of hemodynamic parameters. Rat hearts and sera were preserved for further analysis.

RESULTS
We observed that AP pretreatment dose dependently deteriorated hemodynamic parameters and intensified the degree of injury visualized on light and electron microscopy. It increased the levels of oxidative stress markers in the tissue and cardiac injury markers (CK-MB and LDH) and pro inflammatory cytokines (TNF-α and IL-6) in the sera. Apoptosis was more pronounced in the treatment groups, which was demonstrated using TUNEL assay. They also showed a higher level of pro apoptotic factors (Bax, Caspase 3 and Cytochrome C) and lower level of the anti apoptotic factor Bcl 2. Although AP is known to suppress the NF-κB/TNF-α signaling pathway in states of chronic inflammation such as Psoriasis, we found that NF-κB levels were elevated in the injured myocardium in the AP treatment groups.

CONCLUSION
Apremilast (AP) dose dependently worsens ISO induced myocardial injury. This raises concerns regarding its use in Psoriatic patients with Ischemic heart disease.