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Effectiveness of molecular imaging of programmed cell death with radiolabeled duramycin in focal apoptosis due to myocardial infarction versus diffuse apoptosis in cardiac transplant rejection

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Background: Therapeutic intervention targeted to restrict apoptosis could reduce left ventricle dysfunction. Ergo, noninvasive assessment of apoptosis could be of seminal clinical importance. However, imaging myocardial apoptosis may have differences in feasibility and efficacy when apoptosis is focal (as in the infarct zone) vs. diffuse (as in cardiac allograft rejection). Focal apoptosis imaging using Duramycin can avoid some limitations of Annexin A5 imaging and may be feasible after a major insult like MI, but its comparative efficacy in diffusely distributed apoptosis is unknown.

Purpose: To evaluate the feasibility and effectiveness of imaging apoptosis with a novel method [(99mTc) Duramycin], in experimental models of both focal as well as diffuse myocardial insults that cause apoptosis.

Methods: 2 models were studied:

Protocol A [regional injury after ischemia-reperfusion (IR)] - In an IR injury model in 13 rabbits, 7mCi of 99mTc-labeled Duramycin (n=10; 4 animals treated with an anti-apoptotic agent- minocycline) or 99mTc-Linear Duramycin (a negative tracer control, n=3) were intravenously administered 30 minutes after reperfusion. In-vivo mSPECT-mCT imaging was performed 3 hours after reperfusion followed by ex-vivo imaging of the explanted heart, quantitative assessment of tracer uptake and pathological characterization.

Protocol B [diffuse apoptosis in cardiac allograft rejection (CAR)] - In a CAR model, 16 mice received abdominal heterotopic cardiac allografts (n= 4 each). Group 1: Balb/c donor to B6 recipient (allogeneic transplant, ALO). Group 2: B6 donor to B6 recipient (syngeneic control transplant, CON). Group 3: Balb/c donor to B6 recipient treated with abatacept (allogeneic transplant and immunosuppressed, IMS). Group 4: Bm12 donor to B6 recipient (sub-allogeneic transplant to test for chronic CAR, CHR). Animals were sacrificed at fixed points (ALO and CON 6-7 days, IMS animals 14-15 days and CHR animals 21 days following transplant). MicroSPECT/CT imaging of the heterotopic transplant was performed in vivo and ex vivo after intravenous Duramycin administration for quantitative uptake.

Results: Protocol A - Intense uptake ((%ID/g) of Duramycin was observed in the infarct area (0.751±0.262%) compared to remote area (0.045±0.029%; p<0.01). Minocycline attenuated apoptosis (0.354±0.0624%; p<0.01). Protocol B - CAR animals showed intense uptake in ALO (5.8±2.2), followed by CHR (1.8±1.5), then IMS (1.2±0.4), and CON (0.90±0.04) [p< 0.05 for ALO vs. both CON and IMS groups]. Rejection was ISHLT Grade 3R in ALO, and Grade 1-2R in IMS / CHR groups.

Conclusions Duramycin is similarly effective in imaging apoptotic cell death in localized as well as diffuse myocardial damage and tracks changing levels of apoptosis. Clinical feasibility of apoptosis imaging with a safe PE-seeking antibiotic if proven, might reduce the need for frequent endomyocardial biopsies in patients after cardiac transplant.
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Effectiveness of molecular imaging of programmed cell death with radiolabeled duramycin in focal apoptosis due to myocardial infarction versus diffuse apoptosis in cardiac transplant rejection. The study evaluated the feasibility and effectiveness of using a novel method [(99mTc) Duramycin] in experimental models of both focal and diffuse myocardial insults that cause apoptosis. Two protocols were studied:

Protocol A [regional injury after ischemia-reperfusion (IR)] – In an IR injury model in 13 rabbits, 7mCi of 99mTc-labeled Duramycin (n=10; 4 animals treated with an anti-apoptotic agent – minocycline) or 99mTc-Linear Duramycin (a negative tracer control, n=3) were intravenously administered 30 minutes after reperfusion. In-vivo mSPECT-mCT imaging was performed 3 hours after reperfusion followed by ex-vivo imaging of the explanted heart, quantitative assessment of tracer uptake and pathological characterization.

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Conclusions: Duramycin is similarly effective in imaging apoptotic cell death in localized as well as diffuse myocardial damage and tracks changing levels of apoptosis. Clinical feasibility of apoptosis imaging with a safe PE-seeking antibiotic if proven, might reduce the need for frequent endomyocardial biopsies in patients after cardiac transplant.