ABSTRACT	TITLE	AUTHOR(S)	INSTITUTION	
#12	Comparison of Two Long-acting Injectables in Non-Human Primates with Magnetic Resonance Imaging.	Liza Ganert (1) Julia Rosenberger (2) Andrew Leithead (3) Seth Forster (4) Mona Purcell (5) Joseph Vanderburgh (6) Mark Eric (7)	Merck	Abstract

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Comparison of Two Long-acting Injectables in Non-Human Primates with Magnetic Resonance Imaging

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Introduction

Long-acting injectable (LAI) formulations are designed to maintain prolonged drug exposure while reducing dosing frequency, however little is known about the tissue response over time. Magnetic resonance imaging (MRI) was utilized as a non-invasive method to monitor injection depot formation, volume changes, matrix degradation, and tissue response over time. Two vehicles were evaluated for continuous delivery of a small molecule compound in non-human primates: a conventional polyethylene glycol 300 (PEG300) based formulation and a poly (lactic-co-glycolic) acid in situ gel (PLGA-ISG). The objective was to characterize depot degradation and to provide in vivo insight into the mechanism of prolonged drug release observed with ISG formulations

Methods

Six fasted rhesus monkeys were anesthetized with ketamine (10 mg/kg, IM) and appropriately prepared for two bilateral injections in the scapular region. Each animal received 0.94mL of either PEG300 solution (n=3) or PLGA ISG (n=3) of a small molecule compound and the corresponding vehicle (no compound). One IV catheter was placed in saphenous region for a bolus of Propofol (5mg/kg, IV) for intubation and fluid maintenance (Lactated Ringers at 10ml/kg/hr) throughout imaging procedure. Animals were placed in dorsal recumbency over a flexible imaging coil in a Siemens Trio 3T scanner with dorsal and ventral water heating pads. Anesthesia was maintained on oxygen/medical grade air (70:30 ratio) gas mixture and Isoflurane to effect (1.2-2%) with vital activity monitored and recorded. One hour scans were performed on day 0, 3, 7, and then weekly through week 6, bi-weekly through week 12, and monthly through 16 months after injection. Imaging focused on characterization of depot volume, morphology and local fluid accumulation.

Results

Inflammation of both types of LAI formulations peaked on day 3, while vehicle injections were difficult to palpate. By week 2, signs of inflammation subsided in all animals. No pain management was necessary with continuous evaluation of veterinary staff. The PEG300 formulation formed a relatively homogeneous depot. Depot size decreased monotonically over time, with only minor variation in fluid

content observed within the PEG300 depot. In contrast, the ISG formulation demonstrated a more complex depot evolution. Early in the study, the ISG maintained a stable depot with limited change, potentially protected by a granuloma capsule formation. Over time, likely matrix degradation was observed, accompanied by transient fluid accumulation within the depot, and followed by rapid reduction in volume. In some animals, subcutaneous fat ingress was observed into the granulomatous depot capsule in the last stages of depot degradation. Compared with PEG300, the ISG depot persisted longer before substantial shrinkage occurred, indicating a more durable depot structure.

Conclusions

MRI enabled direct visualization of LAI depots and revealed clear differences between the two formulations in non-human primates. These findings suggest that the novel in situ gel provides a longer-lasting depot than the PEG300 formulation and may be a promising long-acting drug delivery method.