

Ribozyme Pharmacokinetic Screening for Predicting Pharmacodynamics Dosing Regimens

Abstract

There have been only four studies published to date that have addressed locally administered synthetic ribozyme pharmacodynamics in animals. A 2'-O-allyl modified ribozyme targeting amelogenin mRNA inhibited normal enamel formation after submandibular injection in neonatal mice. When injected intraarticularly in the knee, a stabilized ribozyme targeting stromelysin mRNA reduced IL-1-stimulated stromelysin mRNA in rabbit synovium. An anti-protein kinase C α mRNA targeting ribozyme, comprised totally of 2'-amino-modified ribonucleotide analogs, reduced subcutaneously implanted glioma tumor growth in rats. Finally, an in vitro transcribed ribozyme targeting TNF- α mRNA complexes with cationic lipids injected within the peritoneum decreased lipopolysaccharide-induced TNF- α expression in peritoneal cells obtained by lavage. Although this ribozyme was not chemically modified, use of a cationic lipid formulation likely enhanced the circulation time compared with unformulated ribozyme. Unfortunately, no studies have yet been published which explore the treatment of disseminated disease with systemically delivered synthetic ribozymes.

Keywords: amelogenin • ribozyme • TNF- α mRNA • metastasis • angiozyme

Introduction

There are two major VEGF receptor subtypes exist in man (KDR and Flt-1) and, though each receptors seem

to be attached growth, their precise roles during this process are poorly understood. As a result of the potential

role of the Flt-1 receptor in regulation tube-shaped structure assembly and its potential involvement in growth we've developed a changed hammerhead ribozyme (ANGIOZYME™) that targets Flt-1 RNA for malignant tumor applications. The recent advances in ribozyme nuclease stabilization have enabled artificial ribozymes to be considered as potential therapeutic agents [1].

Although several studies have examined the material medica of stabilized oligonucleotides in many species, very little is thought about the pharmacokinetic profile of artificial ribozymes in animal systems. In general, stabilized oligonucleotides are apace distributed following endogenous administration (t_{1/2} α on the order of minutes) with a species and dose dependent ANGIOZYMETM was synthesized in step with the tactic of Wincott et al. ANGIOZYMETM is a 35-mer containing many ester modifications previously shown to reinforce ribozyme stability. For internal labeling with [³³P], ANGIOZYMETM was synthesized in two halves [2].

The 3' half-ribozyme was 5' endlabeled using T4 polynucleotide enzyme and [³³P] ATP. The two half-ribozymes were then ligated along mistreatment T4 RNA ligase. Full

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length internally tagged ANGIOZYMETM was refined from ribozyme halves and unorganized [γ 33P] ATP by polyacrylamide gel di-electrolysis. All studies involving animals were performed in accordance with the National analysis Council's Guide for the Care and Use of Laboratory Animals, USDA regulations, and also the policies and procedures of the RPI Institutional Animal Care and Use Committee. Since the pharmacokinetics of ANGIOZYMETM may well be complications of pathological process un wellness, Lewis respiratory organ malignant neoplastic disease (LLC-HM) tumor-bearing animals were used for this study (see Pharmacodynamics Study Methods). 3 days previous to the initiation of dosing, C57BL/6 mice were inoculated subcutaneously with five x a hundred and five LLC-HM growth cells (kindly provided by Dr. Michael O'Reilly, Harvard University) obtained from growth brief preparations. On post-inoculation day 3, jugular catheters were constituted all told animals. Catheters were connected to subcutaneously constituted Alzet osmotic mini pumps for continuous infusion or were exteriorized for daily bolus ANGIOZYMETM administration. ANGIOZYMETM was administered at a dose of thirty mg/kg/ d supplemented with five x 10⁶ cpm/d ANGIOZYMETM by bolus or continuous infusion. Animals were euthanized by dioxide inhalation fifteen min, four h and twenty three h on days one, 3, 7 and 14 once bolus administration or days one, 3, seven and fourteen once continuous infusion. Blood was sampled via internal organ puncture and supplemental to heparinized tubes. once potential, urine was collected from a glass dish placed at a lower place the animals throughout dioxide inhalation. Tissue as well as thighbone, liver,

lung and growth was collected and forthwith frozen on dry ice. Plasma and tissue were hold on at -70°C until analyzed for ANGIOZYMETM concentrations [3].

Description

On the top of studies demonstrate however pharmacokinetic evaluation will be wont to facilitate optimize the choice of efficacious dosing regimens. In fact, the combination of pharmacokinetic and pharmacodynamics data is particularly necessary once evaluating novel compounds such as ribozymes. The fast in vivo elimination of

Angiozyme couldn't are foreseen supported its substantial in vitro stability in human humor [4].

Conflict of Interests

None

Acknowledgement

None

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