Reversibly Lipidized Interferon-alpha as an Anti-Hepatitis Drug

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Abstract

Reversible aqueous lipidization (REAL) technologies involve the use of novel lipidizing reagents to modify peptides and proteins reversibly. Previously, we have demonstrated that REAL can increase plasma half-life, enhance oral absorption, prolong the therapeutic effects, and alter both biodistribution and elimination of peptide drugs. Recently, we have extended our investigation of REAL from peptides to proteins. Human interferon-alpha (IFN), a 19.2 KD protein containing two disulfide bonds (cys1-cys98; cys29-cys138), was reduced and modified with a reversible lipidization agent. The product of the lipidization, REAL-IFN, was homogenous, with four palmitoyl moieties linked to the four Cys residues in the protein molecule via reversible disulfide linkages. The far-UV circular dichroism (CD) spectrum of REAL-IFN was virtually overlapped with that of IFN, indicating that the IFN structure was not altered by the modification. After *iv* injection in mice at 0.1 mg/kg of REAL-IFN, a low level of serum IFN activity was sustained for more than 8 hours, while serum IFN activity was rapidly diminished to an undetectable level at 2 hours post IFN injection at the same dose. Unlike IFN or pegylated IFN, PAL-IFN was predominately localized in the liver of treated animals. Evidence suggested that IFN was slowly released from REAL-IFN into blood circulation upon reduction of the disulfide bonds *in vivo*, possibly in the liver. Furthermore, the liver-targeting effect of PAL-IFN was demonstrated by the observation that the level of 2'-5' oligoadenylate synthetase (OAS) expressed in the liver of mice treated with PAL-IFN was significantly higher than treatment with IFN. Therefore, REAL technology provides an alternative to pegylation for improving the therapeutic efficacy of IFN for the treatment of hepatitis.

Keywords: reversible lipidization, interferon, hepatitis