

EFdA (Mk-8591, Islatravir) A Very Excellent Anti-HIV Modified Nucleoside, from Design to the Current Clinical Results

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ABSTRACT

EFdA (4'-C-ethynyl-2-fluoro-2'-deoxyadenosine) prevents the emergence of resistant HIV mutants and is over 400 times more active than AZT and several orders of magnitude more active than the clinical reverse-transcriptase (RT) inhibitory 2',3'-dideoxy nucleoside drugs, very low toxic, very long acting, and very useful for prophylaxis.

EFdA is now under clinical investigation by Merck & Co. as MK-8591. In the beginning of my talk, a general idea for the development of anti-viral modified nucleosides based on the mutation of viruses will be presented. Next, the development of EFdA is discussed and then the current results of the clinical trials of EFdA reported by Merck & CO. will be presented. For the design of the modified nucleoside that could solve the critical problems of the clinical drugs (1) Emergence of drug-resistant HIV mutants, (2) Adverse effects by drugs, (3) Necessity to take considerable amount of drugs (4) four working hypotheses were proposed. They are (1) The way to prevent the emergence of drug-resistant HIV mutants, (2) the way to decrease the toxicity of modified nucleosides, (3) the way to provide the modified nucleoside with the stability to both enzymatic and acidic cleavage of glycosyl linkage for long acting in the body, and (4) the different substrate selectivity between RT and human DNA polymerases could enable to develop anti-HIV modified nucleoside that is selectively active to HIV and very low toxic to human beings. 4'-C-Substituted-2'-deoxynucleoside (4'SdN) which has 3'-OH was designed as the nucleoside that could satisfy these hypotheses. The study on 4'SdN has successfully resulted in the development of EFdA [modified at the two positions (2 and 4') of the physiologic 2'-deoxyadenosine] with very excellent anti-HIV activity.

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