

FV100 as a new approach for the possible treatment of varicella-zoster virus infection

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FV100 is a promising new agent with extreme potency and specificity for varicella-zoster virus (VZV). It is the valyl ester pro-drug of Cf1743, the lead clinical candidate among the highly lipophilic bicyclic nucleoside analogue (BCNA) family discovered in Cardiff/Leuven. Cf1743 is unique amongst antivirals in terms of its structure and lipophilicity. It is exquisitely potent and selective for human VZV. FV100 has recently entered a randomized, controlled Phase II clinical trial for the treatment of shingles, sponsored by Inhibitex.

Keywords: Cf1743, BCNA, VZV, antiviral, nucleoside

Introduction

After a primary varicella-zoster virus (VZV) infection the virus establishes latency in the nervous system. Herpes zoster (shingles) represents a reactivation of this virus from latency. Shingles affects ~1 million people per annum in the USA and >100 000 cases per annum in the UK.¹ Of those living to age 85, ~50% will suffer from shingles at some point.² The current antiviral therapy for zoster is based on the acyclic purine nucleoside aciclovir and related famciclovir, and the oral valyl ester pro-drug of aciclovir. These agents are significantly more active against herpes simplex virus (HSV) than VZV and hence their clinical dosing is higher in the zoster setting: in the treatment of shingles in the UK aciclovir is given to adults at 800 mg (5 times daily) and valaciclovir at 1000 mg (3 times daily), each for 7 days.³ These agents have been shown to reduce the duration of viral shedding and hasten healing if dosed within 72 h of the rash appearing.⁴ Antiviral therapy has also been shown to reduce the severity and duration of acute pain, and reduces the risk of long-term pain [post-herpetic neuralgia (PHN)].⁴ While early treatment of the disease is important, for those >50 years of age for whom antiviral therapy was commenced within 72 h, ~20% continue to have pain 6 months after the rash.⁴ There is thus unmet medical need for more powerful and faster acting antivirals for VZV shingles treatment.

Bicyclic nucleoside analogues (BCNAs)

In 1999 while working on an anti-HSV programme between the Welsh School of Pharmacy in Cardiff and the Rega Institute in

Leuven we serendipitously discovered the BCNAs as a new family of highly potent and selective anti-VZV agents. Compound Cf1743, a BCNA with a highly lipophilic pentyphenyl side chain (Figure 1), emerged as the prototype compound, with inhibitory activity against VZV *in vitro* at or below 1 nM concentrations; thus being at least 1000 times more active than aciclovir.⁵ The BCNAs are characterized by a very high lipid solubility leading to a good cellular uptake. They also have an intrinsic fluorescence, making them easy to track into cells or in pharmacokinetic studies. This led us to hypothesize that therapeutic levels may accumulate in cells within minutes of exposure.⁶

The BCNAs have an absolute requirement for VZV thymidine kinase (TK)-mediated phosphorylation for antiviral activity and this in part explains their high selectivity.⁷ They are not recognized by the TK of other herpes viruses such as HSV-1 and HSV-2.⁷ *In vitro* they are non-toxic at the highest concentration available and they also appear non-toxic *in vivo*.⁶

They do, however, have one limitation, which is their water solubility. This is <1 mg/L and impacts badly on the oral bioavailability of these agents. Formulation studies, for example with substituted cyclodextrins, were highly successful at enhancing water solubility, but did not impact positively on their pharmacokinetics (PK), and hence we turned to BCNA pro-drugs.

FV100: the oral pro-drug of the BCNA Cf1743

Several families of pro-drugs were investigated, such as the free 5'-monophosphate, based on the clinical success of the monophosphate of araA (vidarabine) and the cytotoxic nucleoside

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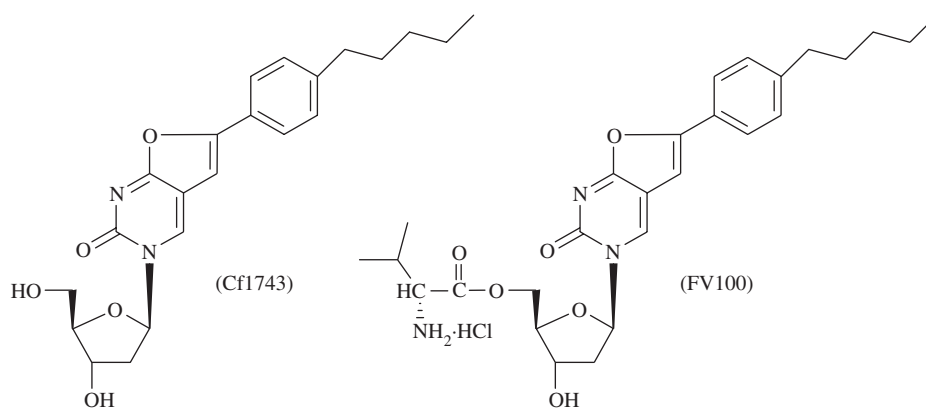


Figure 1. Chemical structure of lead anti-VZV BCNA Cf1743 and its clinical oral pro-drug FV100.

fludarabine. Again, this considerably enhanced the water solubility of the BCNAs, but only slightly enhanced their PK.

Valyl esters of nucleosides are well established as oral pro-drugs, with the aciclovir analogue, valaciclovir, widely used for herpes virus infections such as zoster and the equivalent derivative of ganciclovir being used for the treatment of cytomegalovirus infections.³ Thus, we found that the equivalent 5'-valyl ester of the prototype BCNA Cf1743 greatly enhanced both its water solubility and its bioavailability.⁶ The hydrochloride salt, known as FV100 (Figure 1), was selected as the clinical candidate based on its high solubility (>500 times that of Cf1743), stability and pharmacokinetics.⁶

Mechanism of action

FV100 is considered to act simply as an oral pro-drug of Cf1743 and to lack antiviral effect in its own right. As noted above, the data strongly support the notion of obligate intracellular 5'-monophosphorylation of Cf1743 for biological activity.⁷ However, whether the monophosphate is the pharmacophore, or further phosphorylation, characteristic of nucleoside analogues, is necessary here is currently unclear. Interestingly, when human osteosarcoma (OST) cells were gene transfected with VZV TK, and thus became capable of phosphorylation of the BCNAs, the compounds remained non-toxic, indicating that VZV TK-catalysed phosphorylation of the BCNAs does not elicit a toxic event in cell culture. Notably, a similar experiment with E-5-(2-bromovinyl)-2'-deoxyuridine (BVDU) led to a dramatic increase in cytotoxicity. These data imply that a second viral protein, other than VZV TK, is necessary for Cf1743 to elicit its eventual biological effect. This also implies a high degree of safety for this agent. Further support for this comes from the observation that, again unlike BVDU, the BCNAs are not substrates for human pyrimidine nucleoside phosphorylases (i.e. thymidine phosphorylase).⁸ The free base resulting from BVDU, bromovinyluracil (BVU), has been implicated as the source of (fatal) human toxicity in certain clinical cases in Japan co-treated with sorivudine (BvaraU) and 5-fluorouracil (5-FU). Moreover, the synthetic free BCNA base did not interfere with the catabolism of 5-FU, it did not prove to act as an inhibitor of dihydropyrimidine dehydrogenase (DPD) and did not enhance the 5-FU cytotoxicity *in vitro*, in marked contrast to the situation with BVDU.^{8,9} All of these data suggest a low likely *in vivo* toxicity for the BCNAs.

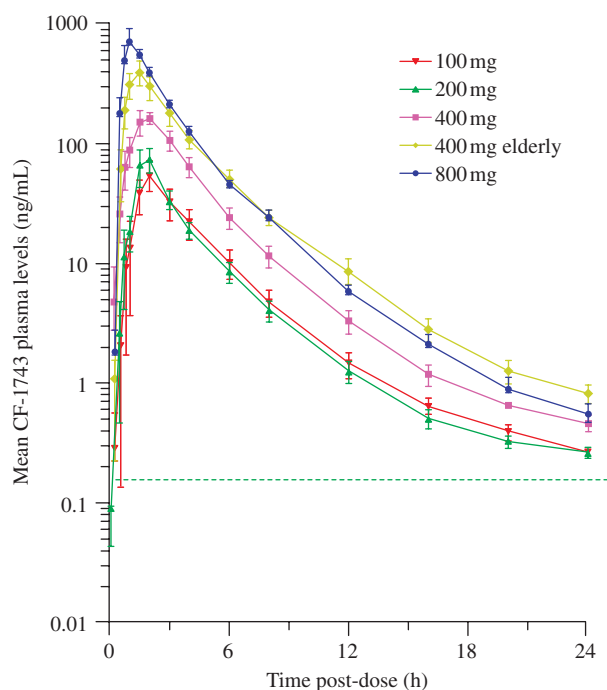


Figure 2. Levels of Cf1743 measured in the plasma of human subjects (means and SDs given) at various timepoints following a single oral dose of FV100 from 100 to 800 mg. The mean EC_{50} value for Cf1743 versus VZV *in vitro* is indicated by the dotted horizontal line. Adapted from Matson *et al.*¹⁰ These data have been presented as a meeting abstract and poster but have not yet been subject to external journal peer review.

Clinical trials

FV100 entered human Phase I trials in 2008, and preliminary data were reported at the International Conference on Antiviral Research, Miami Beach, May 2009.¹⁰ The agent was well tolerated and there were no clinically significant findings for adverse events and clinical laboratory tests. Exposure levels of parent Cf1743 in plasma following a single oral dose of 100 mg of FV100 and above exceeded the effective antiviral level *in vitro* for ≥ 24 h, indicating the possibility of once-a-day dosing of the drug (Figure 2).¹⁰ The appearance of Cf1743 in plasma increased with increasing dose of FV100, and the single

and repeat doses were comparable, indicating a lack of drug accumulation.

Based on these data a controlled randomized Phase II trial was established and began recruitment in May 2009. Valaciclovir at clinical doses is being used as an active control, versus two doses of FV100, given once daily. The projection is that ~330 patients with acute herpes zoster will be enrolled.

Conclusions

Based on the high antiviral potency of Cf1743, and its low toxicity, coupled with the good PK of its oral pro-drug FV100 and known sustained levels of Cf1743 at antivirally effective concentrations it seems reasonable to have a high level of confidence that FV100 has the ability to significantly impact on zoster. Its characteristics are suggestive of a significant enhancement in efficacy over the existing therapies. While the current antivirals for shingles were developed primarily for HSV, and then later expanded to zoster, FV100 represents a new and promising agent specifically developed for VZV. Its structure is unique amongst antivirals as is its exquisite selectivity for VZV. We believe it represents an entirely new and promising strategy for antiviral therapy of VZV.

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Transparency declarations

C. M. is a board member and stockholder of Inhibitex and co-inventor of Cf1743 and FV100. J. B. is co-inventor of Cf1743 and FV100.

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