

## Antivirals: Bindarit – The Future in Alphavirus Treatment

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Chikungunya virus (CHIKV) is an arthropod-borne virus in the *Togaviridae* Family, genus *Alphavirus*. A number of these viruses cause arthralgia and arthritis in humans, including CHIKV, Ross River virus (RRV), Semliki Forest virus, Sindbis virus, o'nyong-nyong virus, and Mayaro virus. CHIKV was first isolated in 1952 in Tanzania [1]. CHIKV infections present with fever, rash and arthralgia leading to arthritis. Its name means “that which bends up”, referring to the stooped posture of patients. There have been numerous outbreaks of CHIKV disease in Asia and Africa: for example, the 2005-06 CHIKV outbreak in La Réunion resulted in approximately 260,000 cases, including 237 deaths [2], and the 2006-07 Indian outbreak had 1.5 million reported cases [3]. Mutations in CHIKV have led to an extension of its vector competence and an increase in its human disease potential. For example, a recently-acquired single mutation in an envelope protein now allows *Aedes albopictus* mosquitoes to transmit CHIKV as well as *Aedes aegypti* [4].

Current treatment is symptomatic, and there are specific therapies available. The recent extensive CHIKV outbreaks have led to renewed interest in CHIKV antivirals, with a number of candidates currently under study. Chloroquine phosphate was reported to be beneficial in CHIKV arthritis [5]. However, this was not confirmed in a subsequent clinical trial [6], and in an animal model of alphavirus infection chloroquine was shown to promote virus replication and enhance disease. Treatment with ribavirin improved the resolution of joint swelling in CHIKV patients [7], and synergy between interferon- $\alpha$  and ribavirin for inhibition of CHIKV replication has been reported.

We have recently discovered that the small-molecule anti-inflammatory drug bindarit is strongly therapeutic in a mouse model of CHIKV infection [8]. Bindarit was also highly effective in treating arthritis resulting from infection with the related alphavirus RRV [9]. In both these models of alphavirus infection, bindarit was able to reduce arthritic inflammation without having any detrimental effect on virus clearance. Bindarit has an innovative mechanism of action (selective inhibition of cytokine/chemokine production, particularly monocyte chemotactic proteins), a substantial and encouraging set of clinical tolerability data (more than 600 subjects, healthy volunteers and patients, treated up to a maximum dose of 2400 mg/day for as long as 6 months), and has the potential to be of benefit in a range of diseases.

Being the most advanced of a group of proprietary compounds acting through a similar mechanism of action; bindarit is currently in clinical development for the treatment of type 2 diabetes nephropathy and for prevention of coronary in-stent restenosis. For rheumatic disease, oral treatment with bindarit confirmed the good tolerability profile of the drug and demonstrated statistically significant effects with a reduction of pain and pannus density. Bindarit was tested in lupus nephritis patients (an orphan drug status was granted by FDA in lupus nephritis) demonstrating a statistically significant reduction of albuminuria. This proof of concept evidence is consistent with animal data showing renal damage reduction and survival increase following bindarit treatment.

More recently, a phase II, double blind, placebo-controlled study was performed in patients affected with diabetic nephropathy. The

findings were promising and based on the results obtained a phase III clinical plan is in place. In addition, a clinical development program in restenosis was designed and a dose-range-finding phase II trial was recently completed.

Chikungunya fever is a global health problem and there is a clear need to develop specific treatment for this disease. Bindarit inhibits inflammatory activity without compromising antiviral immunity, and is now undergoing further development and *in vivo* testing. The utility of bindarit in the treatment of a variety of viral-induced inflammatory diseases is an attractive option.

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