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Preliminary Report of a Controlled Trial of MTH-68/B™ Virus Vaccine Treatment in Acute B and C Hepatitis: A Phase II Study

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Abstract. *Eighty four patients with viral hepatitis attributed to infection with hepatitis B virus (HBV) (n=43) or hepatitis C virus (HCV) (n=41) were included in this study employing the MTH-68/B™ vaccine, an attenuated variant of Bursal Disease Virus. Twenty of the 43 patients in the HBV group, and 22 of the 41 HCV patients were treated with MTH-68/B™. The remaining patients received conventional therapy. Significantly more patients progressed into active chronic hepatitis on conventional therapy (13% of HBV and 26% of HCV cases respectively) than in the vaccine treated groups (0% and 9%). Relapses occured less frequently in the vaccine treated groups (5% of HBV and 32% of HCV) than in the control groups (9% and 79%), while remissions within one month of treatment were observed more often in the vaccine treated groups (both 50% respectively) than in the control groups (26% of HBV and 21% of HCV patients respectively). The duration of hepatitis was also considerably shortened by MTH-68/B™ treatment in both HBV (from 7.5±3.7 to 5.9±3.0 weeks) and HCV patient groups (from 8.9±7.4 to 5.3±4.4 weeks). The data presented suggest that attenuated, non-pathogenic viruses may be of significant benefit for patients with viral hepatitis B and C infections.*

Viral hepatitis is one of the most common infectious disease of humans. It is an inflammation of the liver which is caused by different viruses (hepatitis A, B, C, D, E and G respectively). Based on human studies and animal models of HBV pathogenesis, there is considerable evidence that viral hepatitis is initiated by a specific antiviral cellular immune response, but most of the damage to the liver is caused by a cascade of non-specific effector systems induced by the infection (1). In the majority of cases this disease appears in an acute form, and most of the patients recover completely. Five to 10 percent of acute HBV infections but 60-80% of HCV infections tend to progress into chronic active hepatitis in which the liver cells are gradually destroyed (2). The role of chronic B and C hepatitis in the etiology of liver cirrhosis and various malignancies, including primary hepatocellular carcinoma has been established (3-7). Chronic infection can occur without clinical symptoms of acute hepatitis, since HBV often infects individuals, particularly infants and children, who remain asymptomatic carriers of virus sometimes for decades. Following such an eclipse phase, chronic hepatitis and primary HCC may develop. As the estimated number of HBV carriers is more than 350 millions, it is not surprising that HCC is ranking within the ten most common cancers of the world (8).

The prevalence of hepatitis infection can be significantly decreased by the vaccination of children. Universal vaccination has therefore been adopted in more than 70 countries (9). Although the full efficiency of such vaccination programs on the occurence of hepato-carcinoma will be seen only some 40 years later, it already has been demonstrated in Taiwan that the incidence of hepatocellular carcinoma in children has significantly declined (9).

Until the full effect of such vaccination programs will be felt, however, successful treatment of acute B and C hepatitis remains an important medical problem. Despite significant efforts in the development of treatment strategies for viral hepatitis, as yet there is little that can be done to prevent progression into chronic infection. Treatment of chronic viral hepatitis with interferon-α and other antiviral drugs is not only very expensive, but unsuccessful in many cases. Therefore, it is clear that special efforts must be made to prevent chronic hepatitis (10).

MTH-68/B™ is an attenuated variant of Bursal Disease

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Table I. *Comparison of MTH-68/B™ virus vaccine and conventional treatment of viral hepatitis B and C.*

	Hepatitis B		Hepatitis C	
	Vaccine	Control	Vaccine	Control
Progression into Chronic Active Hepatitis	0/20 (0%)	3/23* (13%)	2/22 (9%)	5/19* (26%)
Occurence of Relapses	1/20 (5%)	2/23 (9%)	7/22 (32%)	15/19*** (79%)
Occurence of Late Remissions (over 6 months)	0/20 (0%)	4/23** (17%)	3/22 (14%)	8/19** (42%)
Remission within 1 month	10/20 (50%)	6/23 (26%)	11/22 (50%)	4/19 (21%)
Duration of Hepatitis (weeks±SD)	5.9 ± 3.0	7.5 ± 3.7	5.3 ± 4.4	8.9 ± 7.4

Significance (p value, chi-square, Yates' correction): *$p < 0.05$; **$p < 0.02$; *** $p < 0.01$)

Virus (BDV), which is a double-stranded RNA virus and a member of the Birnaviridae family (11). As this virus is apathogenic for humans, it has no public health significance (12). An attenuated avian bursa virus was successfully used in the treatment of human hepatitis A viral infection in marmroset monkeys (13). More importantly, when the MTH-68/B™ vaccine has been administered in terminal cancer patients occasionally rapid resolution of viral hepatitis was observed (14). To evaluate the effect of MTH-68/B™ treatment in acute hepatitis B and C, a Phase II trial was conducted data of which are presented here.

Patients and Methods

84 patients of both sexes (ages 14-70 years) with either a diagnosis of acute B (43 patients) or acute C (41 patients) viral hepatitis were included in this study. They were hospitalized because of jaundice, other clinical signs of acute hepatitis (fever, severe malaise, loss of apetite), and a 10-100 fold elevation of alanine-aminotransferase (ALAT) level. The diagnosis of hepatitis B viral (HBV) infection was verified by the presence of HBsAg, HBcAg, and anti-HBcIgM antibody. Acute hepatitis C viral (HCV) infection was determined by the exclusion of A and B virus, EBV, and CMV infection and by the appearance of anti-HCV antibody. Exclusion criteria from this study were the presence of viral markers other than hepatitis B and C, respectively, HIV positivity, suspicion or evidence of alcohol- or drug-induced hepatitis, clinical or histological signs of chronic hepatitis as well as other chronic liver diseases, fulminant hepatitis, malignancies, underlying systemic disease, immunosuppressive treatment within 6 months, pregnancy, and lack of compliance. Patients were randomly allocated into two groups upon admittance. One group was treated with MTH-68/B™ vaccine, while the other received conventional treatment.

The trial protocol was approved by the National Health Scientific Council and the Ethical Committee of St. Làszló Hospital. All patients gave their informed consent. The studies were perfomed according to the Helsinki Declaration of Human Rights. The patients received MTH-68/B™ vaccine, a live attenuated BDV (Phylaxia, Hungary) intranasally once every day (4000 U/day) for 1 week, then 3 times a week for two weeks, and finally once a month for 6 months. Clinical and laboratory investigations were performed before treatment, weekly for one month and once every month for 6 months consisting of physical examination, detection of viral markers, liver function tests (bilirubin, ALAT, ASAT, alkaline phosphatase, γ-glutamyl transferase) and others (ESR, blood count, urinalysis). Liver biopsy was optional (in case of suspicion of chronic hepatitis). Side effects were registered. Criteria of *remission:* normalization of serum bilirubin and ALAT levels, disappearance of HBsAg, no relapse within 6 months; *relapse:* elevation of ALAT (more than two times of upper normal limit) with or without return of jaundice after cessation of therapy within 6 months; subacute course, late *remission:* prolonged elevation (more than two times of normal upper limit) of ALAT after the 6th month of the disease, no viral seroconversion; *chronic course:* more than two-fold elevation of ALAT level after one year, histological signs of chronic hepatitis at percutaneous liver biopsy, HBsAg and/or anti-HBc IgM or HCV-PCR positivity, respectively. Patients with progression into chronic hepatitis and viraemia proven by PCR were treated with interferon-α after one year. Hepatitis serology was tested by commercial enzyme immunoassay kits (Organon and Ortho Microelisa).

Statistical analysis was performed by the Yates' correction of chi-square test.

Results and Discussion

In the present study, an attenuated form of BDV, (MTH-68/B™ virus vaccine) was used for the treatment of viral hepatitis B and C. Consistently with the literature, more patients progressed into chronic hepatitis in the HCV than HBV group. However, there was a significant difference between the vaccine treated and control groups, as only 9% of HCV and none of the HBV patients progressed into chronic disease, whereas 13% and 26% of the controls did (Table I). Prior to complete recovery 9% of HBV and 79% of HCV control patients, but only 5% and 32% of vaccine treated patients relapsed. Late remissions (requiring more than 6 months) were recorded significantly more frequently with conventional treatment in both HBV and HCV hepatitis groups (17% and 42% respectively in controls but only 0% and 14% with vaccine treatment). MTH-68/B™ treatment also shortened the duration of the first icteric phase (by 20% in HBV and 40% in HCV groups). Furthermore more remission within one month of treatment was registered in the virus treated groups (both 50% respectively) than with

conventional treatment (26% and 21%). No side effects of virus vaccine treatment were noted.

It has been shown earlier that concurrent viral infections may significantly influence the outcome of viral disease in humans (15,16,17). Recent studies using transgenic mouse models of the hepatitis B virus infection have revealed how an unrelated viral infection of the liver can be 'curative' to hepatitis B (18). It was demonstrated that hepatocellular HBV gene expression and replication can be abolished by noncytopathic, cytokine-dependent pathway (principally by TNF-α and IFN-α/ß produced by intrahepatic macrophages) which were activated by an unrelated lymphocytic choriomeningitis virus (LCMV) infection of the liver (19). These results imply, that coinfection or superinfection of the HBV-infected liver by other pathogens may facilitate HBV clearance if they induce the local production of cytokines such as IFNγ or TNFα (20). In accordance with this some case report presented evidence that chronic HBV infection resolved during an intermittent infection of the liver by hepatitis A or C (20,21). Conceptually similar events may be operative in other viral infections as well. Indeed, control of viral replication by IFNα/ß, IFNγ and TNFα has been suggested for LCMV, vaccinia, measles, herpes simplex, influenza, Semliki Forest and Theiler's viruses respectively (22-31). It is tempting to speculate that MTH-68/B™ vaccine treatment may resolve the viral hepatitis by a similar mechanism. In conclusion, the MTH-68/B™ virus vaccine therapy reported in this study seems to be safe and efficient in treating acute HBV and HCV mediated hepatitis, thus it may be of significant importance in the prevention of the chronic disease. To reach unequivocal conclusions and possibly elucidate the underlying mechanism of action of the vaccine treatment, we believe, that further investigation is warranted.

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