EPO3267

Use of a vaccinia virus gene product to neutralize interferon-alpha and improve the histopathology of HIV encephalitis in a mouse model

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Background and aims: Interferon-alpha plays a key role in neurocognitive defects associated with human immunodeficiency virus (HIV) and HIV encephalitis. The aim of this study was to assess the effects of a novel inhibitor of interferon-alpha (B18R) in an HIV encephalitis severe combined immunodeficiency mouse model.
Methods: Human macrophages were cultured and infected with HIV-1. Mice (5 week old B6.CB17-Prkdcscid/SzJ) were inoculated with HIV-infected (n=16) or uninfected (n=8) macrophages. The B18R was produced by a modified recombinant procedure. Each B18R treated mouse received 50 mcg per day for 10 days. Brain sections were stained by an immunoperoxidase method. The genes ISG15, IFNA4, and Ifrg15 were analyzed using real-time polymerase chain reaction (PCR).
Results: Gene expression of interferon-alpha signaling was downregulated in the brain by B18R as shown by polymerase chain reaction (PCR). Mononuclear phagocytes were significantly decreased in mice treated with B18R when compared to untreated mice. However, neuronal arborizations were significantly retained in mice treated with B18R when compared to untreated mice. Significant increase in mononuclear phagocytes and loss of neuronal arborization are prominent signs of HIV encephalitis. Findings of this study indicated that the B18R crossed the blood-brain barrier, blocked interferon-alpha signaling in the brain, and improved defects associated with HIV encephalitis.
Conclusion: Findings of this study might suggest that B18R is a potential alternative to monoclonal antibodies used in the management of HIV encephalitis. Further studies are still needed to fully elucidate the effects of B18R in HIV encephalitis.
Disclosure: Nothing to disclose

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A Phase 1 study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of HBM9161 in Chinese healthy volunteers

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Background and aims: Blockade of the binding between neonatal Fc receptor (FcRn) and IgG-Fc reduces circulating IgG, and thus emerges as a potential therapy for IgG-mediated autoimmune conditions.
Methods: This was a double-blind, randomised, single ascending dose study evaluating the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of HBM9161 (a fully human anti-FcRn monoclonal antibody) in healthy Chinese volunteers (NCT03971916). Subjects were given a subcutaneous (SC) dose of HBM9161 340, 510 or 680mg and then followed up for 85 days. Study endpoints included incidence of adverse event (AE), serum drug concentration, IgG, and anti-drug antibodies (ADA).
Results: A total of 24 subjects were enrolled. The observed PK profile is consistent with target mediated drug disposition (Figure 1). The median time to peak serum drug concentration was 36 hours (340mg) and 3.5 days (680mg). A dose-dependent IgG reduction started in 2 days and reached nadir within 2 weeks (Figure 2). The maximum mean IgG reductions were 23% (340mg), 35% (510mg), and 40% (680mg). The recovery of IgG started at Week 3 and returned to baseline by Week 8. All reported AEs were mild in severity. The most frequently reported AEs in the HBM9161 groups were influenza-like illness and rash (Table 1). Only 1 subject was tested ADA positive.

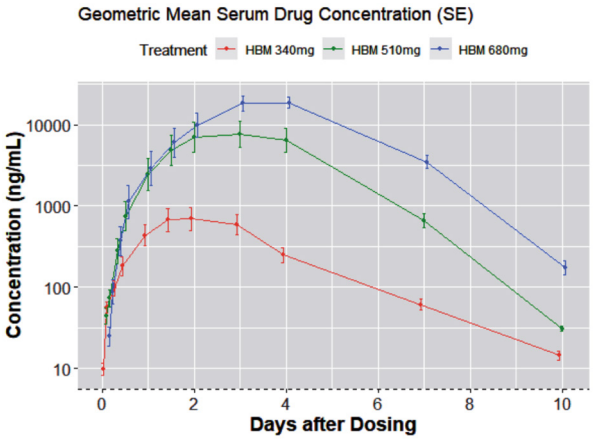

Figure 1. Mean Concentration-Time Profile Following Singe Dose SC Administration of HBM9161