



The Treatment of H5N1 Avian Influenza

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Summary

The intent of this paper is to analyze how current options for treating H5N1 Avian Flu infection may influence the commercialization of the Aethlon Hemopurifier™, a therapeutic device targeted to modulate the immune response and capture circulating H5N1 virus. In the face of an accelerating pandemic, the present void in effective H5N1 treatments may dictate that the Hemopurifier™, initially proposed as a treatment for drug resistant patients, evolves into an important first-line treatment role. Mounting evidence explaining why H5N1 is often fatal to those infected with the virus reinforces the opportunity of the Hemopurifier™ as an essential weapon in the treatment arsenal against Avian Flu.

The Threat

Scientists are increasingly worried that the H5N1 strain of Avian Flu will mutate into a form easily passed between humans, triggering a global pandemic. It already is unprecedented as an animal illness in its rapid expansion, and has cost 300 million farmers more than \$10 billion during its initial spread through poultry around the world. World Health Organization (WHO) officials claim the H5N1 strain of Avian Flu poses a greater challenge to the world than any other infectious disease, including AIDS. WHO officials confirm that 101 of 180 people have died H5N1 infection as of March 15^h, 2006.

In the face of such dire news, researchers are unraveling the mystery of why the H5N1 strain of the Avian Flu virus is so lethal. It appears that H5N1 hyper-activates the immune response, a frightening trait inherent in the worst pandemic killer known to man, the Spanish Flu of 1918, which caused the deaths of over 40 million people. To provide perspective, it has taken 25 years for AIDS related deaths to rise to such levels. In the case of H5N1 infection, viral sepsis leading to major organ failure is often the cause of death. This is triggered when the immune system over-responds to infection by releasing a cascade of inflammatory cells and chemicals in what is known as a “Cytokine Storm”. As a result, the likelihood of death in individuals with robust immune systems equals or exceeds the immune compromised who are normally most susceptible to regular seasonal flu strains. Unfortunately, antiviral drugs are unable to shut off a cytokine storm once it has been triggered.

Current Treatments

Antiviral drugs being stockpiled as part of a global strategy to treat Avian Flu have no therapeutic value once the cytokine storm has been triggered. At present, only one antiviral, oseltamivir (Tamiflu) is known to offer some level of effectiveness against the H5N1 strain of Avian Flu. However, Tamiflu is indicated as a treatment for normal household varieties of influenza if administered within 48 hours of first symptoms. The treatment window for an ultra-virulent H5N1 strain is likely to narrow considerably. Reports already indicate the potency of Tamiflu against the avian flu virus is reduced, even when taken after 24 hours of the first symptoms of the disease. H5N1 resistance to Tamiflu is already being reported in Southeast Asia.

Prolonged incubation combined with a short antiviral treatment window also concerns researchers. Dr. Tim Uyeki, a medical epidemiologist with the influenza branch of the Centers for Disease Control and Prevention (CDC) quoted the following to the Wall Street Journal; “Patients aren’t presenting (symptoms) early in the illness. If the cytokine storm has already been triggered, antiviral drugs aren’t going to turn it off.”

A successful global strategy against H5N1 will, at a minimum, have to rely on therapeutics that can modulate the overproduction of cytokines. The March 2, 2006 issue of *The Lancet* reported that researchers at the well-regarded Karolinska Institute in Stockholm are proposing the use of chemotherapy to kill off excess immune cells as a means to curb the cytokine storm leading to viral sepsis in H5N1 patients. While the concept may seem radical, researchers are likely to agree that any treatment able to damp down the immune system might be helpful. Unfortunately, taming the immune system without destroying defenses against infection has yet to be demonstrated with drugs.

Until other treatments surface, health officials from the United States and other nations continue a strategy of stockpiling Tamiflu. To date, the Department of Health and Human Services (HHS) has ordered 12.4 million doses of Tamiflu, and expects to have a stockpile of 20 million doses by the end of 2006. Adjunctive antiviral therapies able to increase Tamiflu effectiveness will need to surface if these stockpiles are to offer any hope of widespread benefit. Regardless, the effectiveness of Tamiflu and other antiviral drugs ends once the cytokine cascade is triggered.

The Hemopurifier™ to Treat Avian Flu

The Hemopurifier™ is presently the only proposed treatment for H5N1 Avian Flu that simultaneously targets the clearance of H5N1 and the modulation of the cytokine storm. The deployment of the Hemopurifier™ as a treatment for Avian Flu is consistent with a corporate strategy to evolve the Hemopurifier as a broad-spectrum treatment for drug and vaccine resistant pathogens. In this context, the Hemopurifier™ was recently awarded the 2006 Technology Innovation Award by global industry researcher, Frost & Sullivan. Specific to H5N1 infection, the Hemopurifier™ represents a novel extracorporeal method to mimic and boost the immune response, which should improve the effectiveness of antiviral drugs when deployed as an adjunctive therapy. Once a cytokine storm has been triggered, the Hemopurifier could serve as the first and perhaps only option for treating H5N1 infected patients. Attributes and considerations for deploying the Hemopurifier™ as a treatment for pandemic flu, include:

1. **Rapid Clearance of H5N1** - The affinity agents immobilized within the Hemopurifier™ have broad-spectrum capabilities to capture envelope viruses by binding to glycosylated proteins that reside on their surface. In the case of H5N1, the virus capture is directed at two major surface glycoproteins, the hemagglutinin (HA) and neuraminidase (NA), which are available binding sites, even in the case of viral mutation. As compared to normal influenza, longer periods of incubation and accessibility to circulating virus appear to be the norm in H5N1 infection. The ability to clear H5N1 virus and viral fragments prior to cell and organ infection, would decrease cytokine production, inhibit disease progression, and improve the effectiveness of Tamiflu and other antiviral drugs.

2. **Broad Clearance of Cytokines** - The structure of the Hemopurifier™ vastly improves the potential to clear the full spectrum of deleterious cytokines, as compared to Hemofiltration techniques indicated as an adjunct treatment for cytokine induced sepsis since 1990. In fact, the Hemopurifier™ may be an ideal method to modulate cytokine production, as the pores of the Hemopurifier™ fibers are large enough to allow both cytokines and cytokine aggregates, unable to be cleared in Hemofiltration, to be separated and captured from circulation. Non-human studies to document the capture of cytokines, prevalent in autopsy reports of H5N1 induced deaths, have been initiated by Aethlon researchers.

3. **Expedited Regulatory Path** – Under the Bioterrorism Act of 2002, pandemic flu therapies can be developed and financed by the Project BioShield Act. The guidelines require clinical trials to only demonstrate safety in man, as traditional efficacy studies are not plausible or ethical in the case with pathogenic influenza. Thus, the FDA is permitted to accept efficacy data from animal models related to drug and vaccine submissions. In the absence of an animal model, the Hemopurifier™ is positioned to demonstrate the capture of viruses and cytokines from human blood through closed loop studies that replicate human treatment. An Avian Flu Industry Report published by Griffin Securities, suggests that these

regulatory provisions not only provide an accelerated path to approval, but could also provide government funding for stockpiling, representing large commercial opportunities for companies developing Avian Flu therapies.

4. **Human Safety Observations** – H5N1 Avian Flu is not a call to arms to initiate drug and vaccine research programs. It's a siren to deliver therapeutics that are in late stage development and can be delivered to market. The proposed treatment of H5N1 with the Aethlon Hemopurifier™ would be based on treatment protocols already established in a human safety study currently being administered to renal failure patients co-infected with the Hepatitis-C virus. To date, no material adverse events have been observed in these patients. Upon completion of this study, Aethlon will submit the safety data as part of regulatory submissions to the Food and Drug Administration (FDA) in an effort to pursue the treatment of H5N1 Avian Flu and other drug and vaccine resistant viral conditions. The Company may also seek to commercialize the Hemopurifier™ through regulatory agencies outside of the United States.

In closing, the ominous threat of an H5N1 pandemic; the absence of a vaccine; an evolving resistance to a single drug option; and, a post-infection immune response that triggers a highly fatal cytokine storm; provides organizations with innovative therapeutics, the opportunity to demonstrate effectiveness on a global stage. Those who execute and deliver therapeutics to the market will play an important role in saving the lives of individuals infected with H5N1 pandemic influenza.

About Aethlon Medical

Aethlon Medical is developing the first medical device to treat infectious disease. The device, known as the Hemopurifier™, is a broad-spectrum treatment countermeasure against drug and vaccine resistant bioweapons, naturally evolving pandemic threats such as H5N1 Avian Flu, and chronic infectious disease targets including Hepatitis-C (HCV) and the Human Immunodeficiency Virus (HIV). Aethlon has also initiated research on a second generation Hemopurifier™ that targets the capture of growth factors inherent in

the spread of Cancer. More information on Aethlon Medical and the Hemopurifier™ technology can be found at www.aethlonmedical.com.

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