Group A Streptococcus vaccines – considering the issues

LONDON, UK----2 July 2008----ExpertREACT. The highly successful XVII Lancefield conference recently held in Porto Heli, Greece brought together experts in Streptococcal diseases from around the globe. The proceedings continued to remind us of the need for vaccine to lessen the burden of disease caused by Group A Streptococcus (GAS). However, the delegates were also reminded of the significant challenges that lay ahead and the requirement for strategies beyond M-protein candidates coupled with novel clinical trial endpoints

Group A *Streptococcus* **(GAS)** or *Streptococcus pyogenes* is a gram-positive bacterium usually colonizing the human throat and skin without consequence. However, on a global basis GAS is also one of the most frequent human pathogens often placed alongside HIV, malaria and tuberculosis. GAS can cause a wide range of diseases which range from mild superficial epithelial infections e.g. pharyngitis or “strep throat” and impetigo to severe life threatening invasive diseases such Streptococcal Toxic Shock Syndrome (STSS) which can have mortality greater than 35%. Many within the “lay” population have heard of necrotizing fasciitis (NF) or “flesh eating disease” which often accompanies STSS but has even higher mortality of >50%. In the US, GAS is estimated to cause 9,000 – 11,000 cases of invasive disease each year (CDC Figures) and around 15 million cases of pharyngitis.

GAS also causes important post infection non suppurative sequelae such as rheumatic heart disease (RHD) and post-streptococcal glomerulonephritis. In the developing world these diseases exert enormous morbidity and mortality especially in young children (5-15 yrs). For example, in 2005 the World Health Organisation estimated that there were 15.6 million existing cases of RHD with 282,000 new cases each year and close to as many deaths (1). These numbers are probably underestimated especially in less-developed regions where techniques of detection are less established.

The virulence of GAS is directly related to an elaborate array of bacterial surface molecules e.g. carbohydrate and extracellular products including Superantigens that are important to pathogenesis. One of the most prominently studied is the M-protein (*emm*) of which there are over 100-types. Early studies by the pioneering Rebecca Lancefield indicated that GAS strains rich in M-protein were resistant to phagocytosis so paving the way to consider the protein as a possible vaccine antigen. Indeed, studies have shown that antibodies to the M-protein are opsonic, type-specific and long-lasting being able to neutralize the activity of the protein (2). Because certain M-types e.g. M1 and M3 are strongly associated with invasive disease, the proposition to pursue a preventative strategy to also prevent high mortality outcomes has been appealing.

The use of M-protein as a GAS vaccine candidate has not been without challenges. The first consideration has been avoiding the safety considerations of anti-M protein antibodies cross-reacting with cardiac, kidney and CNS based host tissues so in effect replicating long-term sequelae of a natural GAS infection. Many investigators have sought to avoid this “molecular mimicry” by engineering recombinant M-proteins that do not possess the cross-reactive regions and in addition do not activate M-protein specific CD4+ T-cells. Nevertheless, safety concerns will always remain with vaccine candidates needing to undergo extensive in vitro and animal data to prove the absence of cross-reactivity before advancing to the clinic.

Another hurdle in developing M-protein specific vaccines has been wide genetic global diversity and rapid turnover of GAS bacterial strains. Finding a vaccine candidate that would have sufficient strain coverage in both Western and developing regions and maintain its protection will not be easy. Although studies have shown that 10 emm types comprise 86-90% of strains in the US, the same group has also shown wide inter/intra surveillance site variability and temporal variations because the M-protein frequently undergoes genetic recombination (3). The data suggest that harbouring GAS strains could be responsive to immunoselection if a GAS vaccine existed rather analogous to the emergence of non-Prevnar (PCV7) strains in response to conjugate-pneumococcal vaccination.

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Despite these key challenges with M-protein GAS vaccines, a candidate based on peptides from 26 different *emm* types (4 recombinant proteins) known as StreptAVAX did advance to Phase II clinical trials (90 adults) in Canada. StreptAVAX was being developed as part of collaboration between ID Biomedical (later acquired by GSK Biologicals) and the Canadian Centre of Vaccinology. Although the vaccine has been stated to be safe and immunogenic it has been subject to long-term safety evaluation (>1yr) because 5 subjects had minor abnormal cardiac patterns at days 180 after vaccination. A later independent safety review stated the abnormalities were not related to the vaccine and "missed" at baseline but regardless **VacZine Analytics** believes the advancement of the program into children is uncertain for this or other undisclosed reasons.

Other companies have interest in other preclinical GAS vaccine candidates which do not contain the M-protein or contain additional antigens. Notable examples are Novartis Vaccines which is promoting its pillus based technology also part of its Group B Streptococcus work. Novartis states its candidate will enter Phase I in 2010 (4). Wyeth have preclinical interest in Streptococcal C5a peptidase (SCPA) which is expressed by most, if not all GAS strains and may provide cross protection against other beta-hemolytic streptococcal infections. Other companies with IP are Merck & Co, Isconova and Baxter Vaccines.

Beyond the concerns with long-term safety all commercial sponsors face the dilemma of what should be the clinical endpoint in a Western Phase III efficacy trial? The incidence of GAS invasive disease is too low to warrant an economic and feasible study but is a credible selling point for a vaccine. Although the much higher incidence of pharyngitis and/or carriage might more lend itself as an endpoint some argue it will be difficult to justify to regulators unless a robust scientific link to invasive outcomes can be proven. Pharyngitis is not a serious disease but is inconvenient causing many work-days lost for US parents and is estimated to cost US$2 billion of direct healthcare costs (5). A cost-effectiveness case could be built rather like chickenpox vaccination but this is a high hurdle. Lastly, and probably the most relevant to the scientific community, like many other diseases a GAS vaccine should alleviate the enormous impact of the pathogen in the developing world. Could this be achieved by a Western vaccine?

References:

(1) The World Health Organisation (WHO). Current Evidence for the Burden of Group A Streptococcal Diseases (2005).
(2) Lancefield RC. Current knowledge of the type specific M antigens of group A Streptococci. J Immunol 1962; 89:307-13
(3) Shulman ST., Seven year surveillance of Streptococcal pharyngitis emm types in North America. Session 1. 01.3. XVII Lancefield International Symposium on Streptococci & Streptococcal Diseases. Porto Heli, Greece, June 2008
(4) Novartis Vaccines. Corporate Press Release. June 4 2008. Available at: http://www.novartisvaccines.com/press-room/news/20080604_pipeline_vaccines.shtml. Accessed July 2008
(5) Bisno, AL. Acute pharyngitis. N.Engl.J.Med. 2001. 344, 205-11

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