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UNIQUE PATTERN OF INFECTIONS IN CHRONIC GRANULOMATOUS DISEASE – THE ASIAN EXPERIENCE

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Background: Chronic granulomatous disease (CGD) is a phagocytic disorder caused by defective NADPH oxidase activity. Affected individuals are susceptible to bacterial infections, mycosis and hyperinflammatory complications. Variations in the epidemiology of infectious diseases across geographical regions can lead to distinct clinical phenotypes.

Objective: To identify the unique clinical characteristics of a large cohort of CGD patients in China and Southeast Asia referred for genetic studies from 2003 to 2012.

Methods: 53 patients with genetically-confirmed CGD were included and their clinical features were analyzed. CYBB and CYBA mutations were studied by Sanger sequencing, and NCF1 ‘GT’ deletion hotspot mutation was studied on genomic DNA by GeneScan.

Results: 44 patients with X-CGD had CYBB mutations (missense[n=16]; nonsense[n=8]; deletion[n=9]; insertion[n=2]; intron mutation[n=9]). Nine patient had AR-CGD (CYBa[n=5]: NCF1 73-76delGT[n=4]). The median age at presentation and diagnosis was higher in AR-CGD (7m and 66m) compared with X-CGD (3m and 22m). The commonest presentations were pneumonia (58%), skin and perianal abscess (49%), lymphadenitis (42%) and recurrent diarrhea (30%). Aspergillosis and salmonellosis occurred at a frequency similar to published studies (13% and 19% respectively), but the commonest infection was BCG (43%) and 11% had disseminated BCG. 21% of patients had tuberculosis. Fulminant melioidosis and Chromobacterium violaceum infections occurred in 3 patients and two of their male siblings. Hyperinflammatory conditions included polyarthritis (n=3) and pulmonary granuloma (n=2). Death was recorded in 6 patients (15%).

Conclusion: Melioidosis and C. violaceum indigenous to Southeast Asia can cause life-threatening infections in CGD patients. The high incidence of mycobacterial infections is associated with universal BCG vaccination and endemcity of tuberculosis. Such observations emphasize the role of respiratory burst as an immune defense mechanism against these pathogens. These infections are seldom reported in Caucasian cohorts, illustrating the importance of regional collaborative studies to facilitate pattern recognition and early diagnosis of primary immunodeficiencies.

EV71 VACCINE DEVELOPMENT

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Human enteroviruses usually cause self-limited disease except polioviruses and enterovirus 71 (EV71) which frequently cause neurological complications in young children. Due to successful immunization programs, polioviruses are almost eliminated globally. In the contrast, EV71 has recently caused cyclical fatal epidemics in tropical Asia and development of EV71 vaccines has become national priority in several Asia countries. Several vaccine candidates including live-attenuated virus, inactivated whole virus, recombinant proteins, virus-like particles, and nucleic vaccines have been developed and tested in animals. Based on successful experience with inactivated poliovirus vaccines, inactivated EV71 whole virus vaccine candidates are most desirable and five vaccine candidates are being evaluated in clinical trials in China, Taiwan and Singapore. All of these vaccine candidates are inactivated whole virus vaccines but different cell lines and virus genotypes were employed in different organizations. Clinical safety and immunogenicity of several vaccine candidates have been published recently. This presentation will review these data. Moreover, this talk will also discuss international networks for enterovirus surveillance and vaccine quality which are critical to conduct multi-nation clinical trials and the licensure of EV71 vaccines.

AN UPDATE ON THE CURRENT STATUS OF THE DENGUE VACCINE

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Dengue disease represents a growing global threat with an estimated more than 2.5 billion people are at risk, representing more than 40% of the world population. WHO estimates that there are between 50-100 million dengue infections worldwide annually, another 500,000 cases of severe dengue infection with a large proportion of whom are children and about 2.5% of those affected died. This significant disease burden has made the development of an effective vaccine a global health priority.

After nearly 30 years of clinical development and research an effective dengue vaccine has yet to be developed. The first, attenuated tetravalent dengue vaccine was developed at the Mahidol University in collaboration with Aventis-Pasteur in the late 1990s. Phase 1 trial on human volunteers showed preferential viraemia with DEN3 virus and the vaccine was most reactogenic. Since then, newer techniques in the development of a dengue vaccine has enabled a number of manufacturers competing to produce the first dengue vaccine which is not only immunogenic, less reactogenic but efficacious in preventing all four dengue serotypes. Several of the competitors have now reached different phases of clinical trials with the Sanofi Pasteur live, attenuated, chimeric, Yellow fever-Dengue tetravalent vaccine (CYD-TDV) in the forefront of the race completing phases Ib and III of the clinical trials. The vaccine is a recombinant, chimeric vaccine based on the 17D yellow fever virus as its backbone.

Together with the Thai government Sanofi Pasteur had just completed phase Ib efficacy trial (CYD23) of its tetravalent dengue vaccine in 2009. The study involved 4002 healthy children aged 4-11years and was carried out in the Ratchaburi district of Thailand. The results have since been published online in the Lancet in September 2012. The findings of the trial will form part of the discussion in this presentation.