Irrational dengue vaccine designs that ignore IgE and IgG4 mediated effects are destined to follow in Dengvaxia's disastrous direction?

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Oct 2018
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Natural primary dengue infection induces IgE mediated sensitization against dengue antigens.(1,2)

Secondary infection elicits a type 1 IgE mediated immediate hypersensitivity like reaction. A classic type 1 IgE mediated immediate hypersensitivity reaction occurs following an antigen challenge that involves a step change in antigen exposure. Examples include a food allergic person consuming the food allergen. The difference with dengue secondary infection is that the antigen exposure begins at a very low level. As the infection progresses with virus multiplication, antigen exposure ramps up. Hence the antigen challenge in dengue secondary infection is a ramp function rather than a step function. The result is a progressively intensifying allergic reaction that goes from low histamine release induced hives, to high histamine release related high vascular permeability, dengue hemorrhagic fever, hypotension and finally dengue shock syndrome.(3)

We know from food allergy research and helminth infections that once sensitized, continued exposure to that antigen induces an IgG4 response specific to the antigen.(4–9) High IgG4/IgE ratio protects against severe allergic reactions. The IgE dominated aggressive immune response state corresponds to a low level of helminth infection where the body is trying to physically prevent further infection with the itch/scratch responses and mucous secretion. Once infection is established, an aggressive response is life-threatening so the body scales back the response and switches to the IgG4 dominated state. IgG4 dominated response is a low intensity eosinophil mediated chronic battle against the pathogen.(10)

During natural primary dengue infection, the patient is sensitized to the antigens of one serotype at a time. There is now a 25% chance (1 of 4 serotypes) that the next dengue infection can be a serious secondary infection if it is the same serotype.

Given the above, it is easy to see why the quadrivalent Dengvaxia vaccine was a disaster. It caused long term persistent IgE mediated sensitization to all four serotypes and provided short term IgG based protection. Therefore, once protection declines, there's a 100% chance that the next infection will be a serious secondary infection.

While a complete understanding of the immune system may lie deep in the future, vaccine designers seem to be ignoring even what is already known. There seem to be new dengue vaccines which are being developed without understanding the root cause of the Dengvaxia failure.

Natural influenza infection is via the respiratory route. By artificially introducing the influenza virus proteins via the skin/muscle by a subcutaneous or intramuscular influenza vaccine, as is the case for mosquito bite injected dengue virus, we are creating a dengue-like situation for influenza disease also. So we are seeing "cytokine storms" and influenza shock syndrome when the influenza vaccine fails, as previously described.(11)

Following secondary dengue infection, the patient will likely be synthesizing dengue specific IgG4. This reduces the chance of serious future infections. In endemic areas, IgG4 status can be maintained by continuous exposure to infected mosquitoes. If IgG4 levels decline, serious infections are again

possible. Londono-Renteria et al.(9) discuss the bi-specific IgG4 which brings another interesting twist and challenge/opportunity to vaccine design that should not be ignored.

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