Raxibacumab: a panacea for anthrax disease?

When anthrax exposure is suspected, recommended post-exposure prophylaxis is 60 days of antibiotics (ciprofloxacin or doxycycline) combined with anthrax vaccination. Anthrax Vaccine Adsorbed (AVA) is approved for human use in the USA, and Anthrax Vaccine Precipitated (AVP) is approved in the UK. The major antigen in these vaccines is the *Bacillus anthracis* protective antigen; this molecule is secreted by *B anthracis* and creates a pore in the host membrane that binds then separately translocates lethal factor and oedema factor into the cell.[1] Even with prompt antibiotic treatment, the toxins released can still overwhelm the host, leading to toxaemia and death; thus, development and testing of anti-toxin treatments is needed.

US CDC guidelines recommend use of anti-toxin treatments when anthrax exposure is suspected and when antibiotic treatment is contraindicated. The monoclonal antibody raxibacumab has been developed to target the *B anthracis* protective antigen. Raxibacumab binds to the host cell attachment epitope of protective antigen, preventing pore creation.[2] Blocking protective antigen host cell binding prevents both oedema factor and lethal factor from entering the cell, effectively neutralising toxic activity. Protective antigen is also the major protective component of both AVA and AVP vaccines.

Studies in rabbits[3] have shown that polyclonal immunoglobulin purified from plasma obtained after vaccination with AVA and given as post-exposure prophylaxis decreases the protective response of the co-administered AVA vaccine, as measured by anti-protective antigen antibody titres. This effect would diminish the AVA vaccine response when co-administered with raxibacumab. However, in *The Lancet Infectious Diseases*, Nancy Souka and colleagues[4] show in a phase 4 clinical trial that neither anti-protective antigen antibody titres nor toxin-neutralising antibody titres differ between AVA vaccination alone or when raxibacumab is given immediately before AVA vaccination. The findings of this phase 4 study further show that co-administration of AVA with raxibacumab is safe,[4] validating an effective means of defense against acute anthrax.

Whether co-administration of raxibacumab and AVA would prevent anthrax caused by vaccine-resistant isolates is unclear.[5] Raxibacumab treatment of anthrax in animal models has focused on using the *B anthracis* type strain Ames. However, diversity of the *B anthracis* pathogen does exist,[6] and new anthrax-like diseases are evolving in nature.[7,8] Future work investigating the ability of AVA and raxibacumab to prevent anthrax from a *B anthracis* diversity panel consisting of wildlife-outbreak isolates and genetically unique vaccine-resistant strains using an animal model would be of considerable value. Demonstration of anti-toxin efficacy against the *Bacillus cereus* biovar *anthracis*, an anthrax-causing *B cereus* variant, would also be an important milestone for raxibacumab. Although currently isolated to areas in west and central Africa, *B cereus* biovar *anthracis* infects many forest-dwelling primates and farm animals, including goats, cattle, and sheep, in the region;[9,10] while not yet confirmed in humans, new screening could reveal *B cereus* biovar *anthracis* as a source of human anthrax.[11] When *B cereus* biovar *anthracis* is grown in CO_2 or bicarbonate buffering systems, analogous to growth in the host, it expresses genes on the toxin expression pXO1 plasmid to a higher level than does *B anthracis*, indicating a potential for higher toxin production in anthrax caused by this pathogen.[12]

Anti-toxin treatment with raxibacumab is an effective, safe, and valuable addition to the current AVA vaccination regimen for anthrax post-exposure prophylaxis, with the capacity to substantially reduce morbidity and mortality of human infection. However, the broad effectivity of raxibacumab against anthrax caused by new and diverse forms of anthrax pathogens remains to be shown.

We declare no competing interests.

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