Vaccine against hospital-acquired *Staphylococcus aureus*

Kathryn Senior, freelance writer

A Phase III clinical trial has demonstrated that a vaccine containing capsular polysaccharides from *Staphylococcus aureus* (*S. aureus*) confers partial immunity and protection against infection in dialysis patients with end-stage renal disease [1]. The report includes among its authors John Robbins (National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA), who co-developed the effective conjugate vaccine now widely used to protect infants from *Haemophilus influenzae* type b (Hib) infections. 'Making vaccines from capsular polysaccharides is technically difficult, but the effort is worthwhile because they work so well: the new *S. aureus* vaccine has the potential to protect not only dialysis patients, but also people undergoing cardiac and orthopaedic surgery, as well as other at-risk patients,' comments Robbins.

A timely vaccine

An annual death rate of 3–4% attributed to *S. aureus* bacteraemia has previously been reported in patients undergoing regular dialysis [2]. Without an effective vaccine, this is unlikely to improve; as lead author Henry Shinefield, co-director of the Kaiser Permanente Vaccine Study Center (Oakland, CA, USA) points out, 'Antibiotics are becoming less effective as *S. aureus* strains develop resistance to standard therapy with methicillin or vancomycin.'

Testing the conjugated vaccine

Shinefield and colleagues tested a vaccine preparation that included *S. aureus* type 5 and type 8 capsular polysaccharides (CPs) conjugated to non-toxic recombinant *Pseudomonas aeruginosa* exotoxin. 'Conjugation of the polysaccharides to a protein is necessary because the polysaccharides are not sufficiently immunogenic, particularly in immunocompromised patients, such as end-stage renal cases,' explains Robbins. The double-blind trial involved 1804 adult patients in 73 haemodialysis centres in the USA. Each patient was randomly assigned to a single injection of either the conjugated vaccine or saline. All patients were monitored for the production of antibodies specific for *S. aureus* CP5 and CP8 for up to two years, and the incidence of *S. aureus* infection was recorded in the entire patient population over 12 months.

Partial protection achieved

An antibody response of 80 μg ml^{-1} of blood, the estimated minimum level capable of conferring protection in immunocompromised patients, was achieved in 80% and 75% of patients for CP5 and CP8, respectively. *S. aureus* bacteraemia occurred in 11 of 892 patients in the vaccine group, compared with 26 of 906 patients in the control group between weeks three and 40 after vaccination. This gave an estimate of efficacy of 57% (95% confidence limits = 10–81%, P = 0.02). After 40 weeks, the incidence of infection in the two groups was not significantly different; protection was reduced to 23% as antibody levels decreased.

Although this vaccine is the first to show efficacy against an opportunistic pathogen, the results fell just short of the original goal of showing effectiveness at 54 weeks after vaccination, and the US Food and Drug Administration (FDA) has requested another Phase III trial before considering approval. Robert Naso, Senior Vice President of Nabi (Rockville, MD, USA), the company co-developing StaphVax™, confirms that a second Phase III trial is scheduled to begin by spring 2003. 'We plan to recruit 2700 end-stage renal dialysis patients, of whom half will receive StaphVax and half placebo, and the primary clinical endpoint will be protection at eight months post-vaccination,' explains Naso. It has not yet been decided whether to provide a booster injection in the expanded trial: Nabi is currently discussing the issue with the FDA and an interim booster trial of 77 subjects from the first Phase III trial is currently under way. 'We expect safety and immunogenicity results from the booster study by the end of June 2002,' says Naso.

Are proteins important?

Jean Lee (Channing Laboratory, Harvard Medical School, Boston, MA, USA), author of a recent review on the different developmental strategies being used to make staphylococcal vaccines [3] thinks that the results with CP5 and CP8 are 'very promising and original'. Several other researchers interested in a staphylococcal vaccine have focused on adhesins, bacterial surface proteins that are believed to mediate the attachment of *S. aureus* to host matrix-proteins, such as fibronectin, fibrinogen and collagen. 'Antibodies to fibronectin-binding protein A, clumping factor, and collagen binding protein have been shown to protect animals against experimental *S. aureus* infections, but human clinical

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trials have not yet been performed,' she explains. Lee suggests that perhaps adhesins could be used as the protein component of a conjugate vaccine coupled to CP5 and CP8 to see if a multicomponent vaccine would be more effective.

Although there are no plans to include staphylococcal proteins, a future generation of the CP vaccine is likely to include an extra polysaccharide. 'The original vaccine, which had just CP5 and CP8, protects against ~85% of all clinically significant *S. aureus* isolates, but inclusion of the recently discovered type 336 should increase this to almost 100%,' says Naso. Lee is less convinced about CP336. 'The composition of the CP336 polysaccharide has not been published, nor have these investigators demonstrated that antibodies to CP336 are protective against *S. aureus* infections,' she points out. Naso, however, counters that Nabi has received a US patent on the CP336 antigen based on both structural data and animal studies and the group is confident that these three CPs should cope with all *S. aureus* infections. 'Other capsular antigens could be added to subsequent generations of the vaccine to address other pathogens such as *Staphylococcus epidermidis* and enterococci,' he adds.

The future

Safety and immunogenicity studies of StaphVax are also planned for other at-risk patient populations. 'If the first-generation vaccine can protect dialysis patients who are immune-compromised and at long-term risk of staphylococcal infections, then the vaccine is also likely to protect against *S. aureus* bacteraemia in more healthy at-risk populations, such as those receiving medical implants, the elderly in extended care facilities, and even surgery patients,' predicts Robbins.

References

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Caspase inhibitors for liver disease

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A drug that inhibits apoptosis could be used to treat a range of liver diseases. IDN6556 has been found to be safe and well tolerated in a recent Phase I study, and will soon enter Phase II trials in patients with liver impairment.

Apoptosis is caused by a cascade of intracellular cysteine protease enzymes called caspases (Fig. 1). Too much apoptosis plays a part in conditions as diverse as ischemic injury, neurodegenerative diseases, inflammatory diseases, osteoarthritis, allograft rejection and septic shock. Conversely, insufficient apoptosis is implicated in cancer and autoimmune disease. There is, therefore, great interest in finding drugs to manipulate the pathways that control cell death, and many such products are in clinical trials [1].

Excessive apoptosis also occurs in various liver diseases, including alcoholic hepatitis, hepatitis B and C, Wilson's disease and drug-induced hepatotoxicity [2]. Treatment is problematic: severe acute alcoholic hepatitis is fatal in >50% of cases. Hepatitis C is treated with α-interferon, but this is only effective in ~50% of patients and is expensive.

Broad spectrum

Idun Pharmaceuticals (San Diego, CA, USA) is developing a caspase inhibitor known as IDN6556 that it hopes will prevent liver degeneration by blocking cell-death pathways. In conditions such as acute alcoholic hepatitis, cytokines such as tumor necrosis factor-α (TNF-α) are produced in the liver and bind to so-called 'death receptors' on the surface of hepatocytes. This activates caspase 8, which in turn cleaves and activates the effector caspases – those proteases that bring about the lethal events characteristic of apoptotic cell death [2].

IDN6556 is a small molecule that binds irreversibly to the cysteine residue at the active site of several caspases. 'IDN6556 is designed to inhibit both the initiator caspase, namely caspase 8, and also the downstream caspases in case there is any leak-through,' says Kevin Tomaselli, co-founder and Vice President of Discovery Research at Idun. It is the first broad-spectrum caspase inhibitor to be tested in humans. 'The broad spectrum of action is also advantageous because there are two caspase pathways controlling apoptosis, and we do not yet know which [pathway] is at work in particular disease situations, or whether it is both,' Tomaselli explains. 'With a broad-spectrum drug we can hit both pathways.'

The therapeutic potential of caspase inhibitors in liver disease was demonstrated in studies with a prototype broad-spectrum caspase inhibitor, IDN1965 [2]. Apoptosis-associated liver injury can be induced in mice with anti-Fas antibody.

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