Researchers identify new target to treat bacterial keratitis from contact lenses

A new approach to tackling bacterial keratitis has shown encouraging results in a series of early stage studies.

This novel approach targets specific proteins in the host rather than in the bacterial pathogen itself. Given the significant emerging problem of antibiotic resistance, such a strategy may provide a valuable tool in the clinicians’ ability to limit corneal damage from infectious agents such as Pseudomonas aeruginosa.

The potential market for products to treat bacterial keratitis is immense. Corneal infections associated with contact lens use are well established. By one estimate, one in 2,500 daily-wear contact lens users and one in 500 extended-wear contact lens users develop bacterial keratitis each year.

The new research, undertaken at the Wayne State University School of Medicine in the American city of Detroit, was led by Dr Archana Thakur and Dr Linda D. Hazlett.

The researchers’ novel treatment targets one of a group of proteins called “cytokines.”

Cytokines are known to play a significant role in initiating and sustaining inflammation in a wide range of diseases. The results of the research appear in Investigative Ophthalmology and Visual Science, 2004;45:3177-3184.

One of the key complications of bacterial keratitis is the potentially severe corneal ulceration and scarring brought about by the body’s attempt to rid the cornea of the bacteria.

A strategy that targets a specific cytokine, known as IL-1ß converting enzyme, or “ICE” for short, is designed to dampen down the potent chemical armamentarium used by the body to defeat the bacterial pathogen.

In some instances, it is the body’s response to infection that causes the majority of tissue damage rather than the actual infection itself; infections of the cornea by Pseudomonas aeruginosa provide one example of such a phenomenon.

ICE is well known as a potent pro-inflammatory cytokine involved in both the initiation and amplification of inflammatory and immune responses including the activation of a broad range of immune defence proteins.

Downstream effects of ICE activation include the recruitment of specialised immune cells to an infection or wound site. Although the exact mechanism of host-mediated corneal destruction in bacterial keratitis is un-proven, it has been postulated that an imbalance in a number of downstream immune defence proteins activated by ICE might lead to destruction of corneal connective tissue.

Previous studies by different research groups had established a link between the severity of a corneal infection and the relative concentration of ICE. The clear rationale in the approach of Dr Thakur and Dr Hazlett was to determine if an inhibitor of ICE – which is manufactured by the American-based Vertex Pharmaceuticals – was capable of reducing the levels of ICE in the cornea with the intended outcome of reducing the severity of disease.

Keratitis resulting from infections of Pseudomonas aeruginosa may account for as much as one-third of microbial infections associated with contact lenses wear. The general management of such infections is geared toward killing off the bacterium and limiting the body’s own destructive immune response through usage of corticosteroids.

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However, “the effect (beneficial or detrimental) of corticosteroids in reducing host mediated tissue damage has not been proven conclusively in bacterial keratitis,” the doctors observed. “Therefore, the controversial role of corticosteroids and emerging resistance of Pseudomonas aeruginosa to antibiotics warrant development of new adjunctive therapeutic modalities.”

The researchers also tested an inhibitor of ICE in a mouse model following infection with Pseudomonas aeruginosa. The tests were carried out in conjunction with or without ciprofloxacin, an antibiotic which interrupts bacterial multiplication.

A small inoculum of about 1 million Pseudomonas aeruginosa bacteria were delivered topically to the left cornea of test animals followed 18 hours later by a sub-conjunctival injection of ICE inhibitor. Various amounts of ICE inhibitor were tested ranging from 30 µM to 1,000 µM formulations but the optimal efficacy was observed with 300µM doses. Animals were examined at 1, 3, 5, and 7 days post-infection; the researchers also performed a number of assays to determine the effect of ICE-inhibitor administration.

Clinical analysis of corneas following treatment with ICE inhibitor demonstrated a significant decrease in disease severity when compared to placebo-treated controls for up to seven days post treatment. Additionally, slit lamp microscopy of the cornea revealed significantly less immune cell infiltration in ICE-inhibitor treated subjects compared to placebo controls that exhibited clear corneal perforation.

Histopathology of treated versus placebo corneal tissue showed that there was a minimal anterior chamber inflammatory response in ICE-inhibitor treated eyes compared to placebo treatments. According to the researchers, those corneas treated with the placebo showed “a heavy cellular infiltrate in the cornea with complete denudation of the corneal epithelium, central stromal degradation, severe oedema, severe anterior chamber inflammation, and perforation.”

The research of Dr Thakur and Dr Hazlett showed that the ICE inhibitor alone could not stop inflammation or reduce its levels as much as could be achieved through use of the antibiotic ciprofloxacin. However, subjects treated with the ICE inhibitor were able to slow the progression of the disease and prevent corneal perforation.

Crucially, researchers were able to quantify the reduction in the concentration of ICE between ICE-inhibitor treated and placebo subjects to establish that ICE concentration had been reduced by approximately 75%. The knock-on effect of reduced ICE presumably suppressed a number of the immune responses brought about through immune cell infiltration to the infection site in addition to suppressing down stream activation of a range of immune biochemicals which can contribute to inflammation, ulceration and scarring.

The research results represent an encouraging advance in the development of future therapeutic regimens to tackle Pseudomonas aeruginosa and possibly several other microbial infections. Without the proper and timely treatment of such infections, disease can progress quite rapidly leading to a permanent loss of vision from corneal scarring.

“Treatment with the ICE inhibitor was most efficacious in adjunctive therapy to complement the bacterial killing effects of ciprofloxacin and, together with the antibiotic, synergistically appeared to down regulate the host inflammatory response better than use of either of the agents alone,” the researchers concluded.

“Treatment with the ICE inhibitor also contributed, indirectly, to lessening bacterial growth” (as it had no ability to kill bacteria), perhaps because bacteria are not able to disseminate in a cornea in which damage is reduced.”

Glossary

µM: measurement denoting a concentration of 10^-6 mole per litre

Antibiotic resistance: the ability of a bacterium to mutate and synthesise proteins to counter the effects of antibiotics

Corticosteroids: a group of synthetic steroids used in the medical treatment of certain leukemias or to suppress graft rejections in transplant surgery; side effects include an increased risk of infection

Cytokines: a class of proteins secreted mostly by specialised tissues or cells of the immune defence system, they act locally in a cell signalling role in comparison to for example, hormones which act at a distance from the point at which they are produced

Host: an organism that is infected with a pathogen or parasite such as flu virus or HIV

Host-mediated: occurring due to activities of the host itself rather than a direct effect of a pathogen

Inoculum: cells used to start a culture or infection in a host.