Medical Countermeasures to Address Intracellular Bacterial Pathogens

The Efficacy of Finafloxacin Against Biological Threat Agents

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Antimicrobial resistance is a global problem causing concern in the clinical environment where a number of infections are becoming difficult to treat with the currently available antibiotics, in particular the fluoroquinolones. In addition, the biological threat agents are organisms that can reside within a number of different types of cell, their life cycles relying on intracellular replication to survive and proliferate. They are protected from the host response and antimicrobial treatment is dependent on the ability of antibiotics to penetrate cells and remain active in the conditions encountered within these cells. The antibiotics available to treat infection with the biological threat agents are limited, not completely effective and there is the possibility that naturally or genetically engineered resistance may become a problem in the future. Thus, to ensure military operational effectiveness in the event of a deliberate release, identifying antibacterial medical countermeasures that show an improvement or advantage (for example, in protection or regime) when compared to the currently fielded antibiotics is a high priority.

Finafloxacin is a novel fluoroquinolone developed by MerLion Pharmaceuticals that has been chemically manipulated to engineer enhanced activity under acidic conditions, where other fluoroquinolones, including ciprofloxacin, are significantly less activated. Therefore, finafloxacin may exhibit advantages over other fluoroquinolones when treating infections caused by bacteria that reside within acidic cellular organelles, including the biothreat agents. An oral formulation of finafloxacin is available and have been utilised in Phase Iia studies, aiming to eradicate Helicobacter pylori in uncomplicated urinary tract infections.

Dstl, in collaboration with MerLion Pharmaceuticals, have shown that finafloxacin is rapidly bactericidal for Burkholderia pseudomallei, Franciscella tularensis, Yersinia pestis, Bacillus anthracis, Burkholderia mallei and Coxiella burnetii, activity which is significantly enhanced at pH 5 compared to pH 7. Finafloxacin has also demonstrated significant protection against inhalational infections of B. pseudomallei, F. tularensis and C. burnetii in murine models. Recently acquired DTRA funding will further determine the utility of finafloxacin, initially focused on the treatment of infection caused by B. pseudomallei, investigating the window of opportunity for initiating treatment, the effect of shortening the treatment regime and combining finafloxacin with other antibiotics. In addition, the broad spectrum efficacy of finafloxacin against aerosol infections of F. tularensis and Y. pestis will be evaluated in vivo. Data generated in this project will be used to inform the defence organisations to enable the use of finafloxacin in the armed forces in the event of a biological release, and will also contribute to the data package required for licensure.

Consequently, finafloxacin is a promising medical countermeasure for use in the event of a deliberate release of biological threat agents; therefore, further investigation of finafloxacin is warranted.

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