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TRIAL WATCH

Phase III success for novel *Clostridium difficile* antibiotic

The results of the second of two Phase III trials evaluating the macrocyclic antibiotic fidaxomicin (OPT-80, PAR-101), developed by Optimer Pharmaceuticals, confirm that it is as efficacious as vancomycin for treating patients with *Clostridium difficile* infection (CDI). It is also associated with a lower incidence of recurrence of CDI.

The study, which involved 535 adult patients, met the primary end point of non-inferiority to vancomycin, with a 10-day course of oral fidaxomicin achieving clinical cure in 91.7% of patients versus 90.6% in vancomycin-treated patients. Secondary end points were also met: 4 weeks after therapy, there was less recurrence of infection in fidaxomicin- versus vancomycin-treated patients (12.8% versus 25.3%, respectively). In addition, the global cure rates (defined as patients who were cured and did not have a recurrence) were higher in fidaxomicin- versus vancomycin-treated patients (79.6% versus 65.5% of patients, respectively). The study also reported that the antibiotic was well tolerated and safe.

C. difficile is a Gram-positive anaerobic bacterium that colonizes the lower gastrointestinal tract, where it produces toxins that cause inflammation, abdominal pain, diarrhoea and sometimes colitis. CDI may result from the prolonged use of broad-spectrum antibiotics, causing a disruption of flora homeostasis in the gastrointestinal tract. Outbreaks of CDI also commonly occur in hospital environments, particularly in the elderly. Recurring infection with *C. difficile* and the emergence of several drug-resistant strains has led to its treatment becoming increasingly difficult. Moreover, the current CDI therapies, vancomycin and metronizadole, are also limited by relatively high relapse rates and side effects.

"The two major challenges in therapy for CDI are to cure episodes of severe disease and to prevent relapses occurring following initial cure," notes Ian Poxton, professor at the Centre for Infectious Diseases, University of Edinburgh, UK. "Preventing a primary episode of disease in an at-risk patient is best done by restoring the normal microbiota to 'normality' or preventing its disruption during broad-spectrum antibiotic treatment," he adds. Several treatment approaches are being investigated, although they have limitations. "Unfortunately, probiotics have so far been disappointing. However, a promising treatment approach is immunotherapy using monoclonal antibodies, as a failure to mount an appropriate antibody response may be an important risk factor. In addition, while the use of active vaccination is theoretically attractive, it may not produce protection in the susceptible host," says Poxton.

Fidaxomicin has the potential to address some of these challenges. "It is a novel macrocyclic antibiotic, which specifically prevents bacterial transcription by inhibiting bacterial RNA polymerase," explains Grit Ackermann, M.D., Medical Cooperation for Laboratory Diagnostic and Medical Microbiology, Leipzig, Germany. "Compared with other antibiotics, fidaxomicin shows only low systemic absorption, high faecal concentration and, due to its narrow spectrum of activity, targets only Gram-positive aerobic and anaerobic bacteria, with almost no alteration of the normal intestinal flora," says Ackermann. "These characteristics and the study results suggest that this agent has the potential to be incorporated into the guidelines for CDI treatment, and the favourable relapse rates compared with vancomycin may result in the recommendation to use fidaxomicin first line," concludes Ackermann.

However, several questions remain: "The big unknown is whether resistance will occur and if it does, how quickly," notes Poxton. So far, *in vitro* studies show promising results, with fidaxomicin exerting a low frequency of spontaneous resistance or cross-resistance with several other antibiotics. Poxton also cautions that fidaxomicin is currently proposed as an oral agent, and so delivery to the site of infection in the severely ill patient with CDI is likely to be difficult. Optimer plans to submit a new drug application to the FDA in the second half of 2010.