EDITORIAL

Cryptosporidiosis: the treatment dilemma

Cryptosporidiosis, caused by infection with the protozoan parasite *Cryptosporidium parvum*, was first recognised as an intestinal disease entity in man in 1976, but ascended to even greater medical importance in 1982 with the advent of the AIDS epidemic [1]. In immunocompromised patients, and particularly those with the human immunodeficiency virus (HIV), persistent diarrhoea, malabsorption, weight loss and even death result from infection [2, 3]. Symptoms often parallel the progression of AIDS, with the most severe observed in those with CD4 cell counts $<50/\text{mm}^3$ [4]. The elderly and immunologically naïve, including malnourished children, also may suffer severe disease directly related to infection with *C. parvum*. However, most attention has been directed to the AIDS group in attempts to resolve this infection.

An early assumption was that *C. parvum*, being a coccidian parasite, would respond to conventional anticoccidian therapies [5]. However, a decade and a half of intensive testing in vitro and in vivo of >100 chemotherapeutic agents has yielded more frustrating than promising leads [6]. Many have ascribed this to the parasite's unique intracellular, but extracytoplasmic location [4]. This habitat is established following parasite invasion of enterocytes and leads to the parasite being bound apically by a vacuolar membrane of presumed host cell origin and distally by an elaborate folded membrane, the feeder organelle, which is in direct contact with the host cell cytoplasm. It has been proposed that this latter site might regulate nutrient or drug access to the parasite. Recently, a parasite-encoded transport protein has been localised at the parasite–host cytoplasm interface and may represent a potential drug target for future investigation [7].

In spite of the numerous failed attempts to treat cryptosporidiosis in AIDS patients, encouraging results have emerged from treatments with paromomycin [8], the combination of paromomycin plus azithromycin [9], and nitazoxanide [10]. Paromomycin is an aminoglycoside that has shown variably positive results when given orally to AIDS patients with cryptosporidiosis. It is not absorbed well by host cells, but apparently can be absorbed in small quantities across the limiting apical membrane bounding the extracytoplasmic parasite [11]. When given alone, relapse is common and the drug may be ineffective against biliary and pancreatic infection. In one study, the

activity of paromomycin was enhanced when given concomitantly with the macrolide (azalide) antibiotic, azithromycin [9]. However, improvements in parasite excretion and stool frequency were not always accompanied by consistent reductions in stool volume and it was noted that the drugs themselves might have contributed to worsening diarrhoea or gastrointestinal functioning. Also, biliary disease remained a problem.

Rather dramatic treatment results in AIDS patients with cryptosporidiosis have been reported in a placebo-controlled trial of nitazoxanide, a nitrothiazole benzamide that has a wide spectrum of activity against various bacterial, protozoal and helminth pathogens [10]. While results appeared to be statistically significant compared with controls, there was still a 25% cure rate in the placebo group. Moreover, the trial had certain weaknesses: patients receiving therapy were not stratified by CD4 counts; they were not excluded if they had concomitant enteropathogens; and the period of follow-up after treatment was short. Clinical trials with this drug in the USA had to be discontinued because of the impact of combination antiviral therapies on the incidence of opportunist infections in patients with AIDS, which has led to a marked decline in those being enrolled. The US Food and Drug Administration (FDA) declined to recommend accelerated approval of the use of nitazoxanide in May 1998, citing problems with baseline data, efficacy endpoints and the need for further trials with different study designs [12]. It was also noted that the mechanism of action of nitazoxanide is not known and its pharmacodynamics are incompletely understood. In spite of this, nitazoxanide has de facto become the drug of choice because of availability through various AIDS patient networks [12].

The problem with cryptosporidiosis in AIDS patients and the lack of approved or totally effective therapies has sparked interest in the use of polyclonal antibody-based immunotherapies in this condition [13]. The basic strategy is to develop high titre antibody solutions that would effectively neutralise selected stages in the life cycle of the parasite by preventing them from attaching to and invading host cells. Encouraging results were observed in very preliminary studies of oral administration of hyperimmune bovine colostrum [14, 15]. However, follow-up clinical studies with the bovine antibodies [13] or hyperimmune egg-yolk

antibodies (Dr R. Soave, Cornell University Medical College, personal communication) have shown variable clinical benefits ascribed to treatment. Further success with such products might be achieved by developing improved formulations that would survive passage through the intestinal tract and be better retained at the required site of action. This approach has, in turn, prompted research into formulating specific monoclonal antibodies that alone or in combination with others might be used as oral immunotherapy. To date, such antibodies have shown promise, but only in vitro and in animal models of cryptosporidiosis [13].

The dilemma is that as yet there is no totally effective and approved therapy for cryptosporidiosis, either in AIDS patients or other affected populations. Furthermore, combination therapies available to AIDS patients have minimised the extent of the problem in developed countries to such a degree that it has been difficult to enrol enough patients to conduct meaningful clinical trials with new products. This, and the de-facto use of nitazoxanide, might serve to lessen interest in the development of new products by pharmaceutical companies. However, recent articles in the American media have reported a lessening in the sharp decline of AIDS deaths, suggesting that antiretroviral therapies might be losing their effectiveness. If true, this would represent a major setback to HIV therapy and to the control of opportunist infections in these patients.

A factor that is frequently overlooked is that the vast majority of individuals in the world with AIDS do not have access to antiretroviral therapies. These individuals also do not have access to therapies that might show even partial efficacy against cryptosporidiosis. Also largely overlooked is the impact of cryptosporidiosis on children in developing countries and the need to consider some form of therapy, other than oral rehydration, in dealing with this situation. Results of one study indicate that infection with *C. parvum* in very young children has an adverse impact on their growth and subsequent ability to catch up [16]. This situation was exacerbated for children with a poorer nutritional status. Intervention strategies, including specific therapy, might correct this problem. Other potential beneficiaries of a specific therapy might include individuals exposed to cryptosporidium infection through waterborne outbreaks, outbreaks in day-care centres and through frequent contact with animals. There may even be a need for a specific treatment or prophylaxis in certain animal species in which the young are particularly prone to disease caused by *Cryptosporidium*.

C. parvum has proven to be a formidable foe. One concern is that the pharmaceutical industry will lose interest in developing therapies against an organism that has been so intractable. Moreover, the market for a specific therapy against cryptosporidiosis is relatively small and the financial rewards for developing a new

product would probably be minuscule. However, it is clear that cryptosporidiosis remains a problem and that research into developing new treatment and prophylactic strategies must continue. A better understanding of the organism's biology is likely to lead to a more rational, rather than an empirical, approach to drug development and testing. This approach should not discount the potential for antibody- or immunomodulatory-based therapies.

CHARLES R. STERLING

Department of Veterinary Science and Microbiology,
University of Arizona,
Building 90, Room 202,
Tucson, AZ 85721, USA
(e-mail: csterlin@u.arizona.edu)

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