Experimental Parasitology 124 (2010) 45–53

Contents lists available at ScienceDirect

Experimental Parasitology

journal homepage: www.elsevier.com/locate/yexpr

Cryptosporidium and *Giardia*: Treatment options and prospects for new drugs

Jean-François Rossignol [1]

Division of Gastroenterology & Hepatology, Department of Medicine, Stanford University School of Medicine, Pasteur Drive MC: 5187, Room 3115A, Stanford, CA 94305-5187, USA
The Romark Institute for Medical Research, Tampa, FL 33607, USA

ARTICLE INFO

Article history:
Received 18 October 2008
Received in revised form 2 June 2009
Accepted 3 July 2009
Available online 24 July 2009

Keywords:
Cryptosporidium
Giardia
Treatment
Nitazoxanide
Nitroimidazoles

ABSTRACT

Cryptosporidium species and *Giardia intestinalis* are the most common enteric protozoan pathogens affecting humans worldwide. In recent years, nitazoxanide has been licensed in the United States for the treatment of cryptosporidiosis in non-immunodeficient children and adults, becoming the first drug approved for treating this disease. There is a need for a highly effective treatment for cryptosporidiosis in immunodeficient patients, but the quest for such a drug has proven to be elusive. While not effective against *Cryptosporidium*, nitroimidazoles such as metronidazole or tinidazole are effective treatments for giardiasis and can be administered as a single dose. Albendazole and nitazoxanide are effective against giardiasis but require multiple doses. Nitazoxanide is the first new drug developed for treating giardiasis in more than 20 years. New potentially promising drug targets in *Cryptosporidium* and *Giardia* have been identified, but there appears to be little activity toward clinical development of new drugs.

1. Introduction

Cryptosporidium spp. and *Giardia intestinalis*, the most common enteric protozoan pathogens affecting humans, are important causes of morbidity in developed and developing countries. These organisms primarily affect the small intestine causing persistent diarrhea and enteritis. There are, however, considerable phylogenetic and physiological differences, and there have been considerable differences in the activities of chemotherapeutic agents against these organisms.

The recent licensure and introduction of nitazoxanide (Fig. 1) is an important advance in that it is the first drug for treatment of cryptosporidiosis and the first new drug for treating giardiasis in more than 20 years.

2. Cryptosporidiosis

Cryptosporidium was discovered by Tyzzer in 1907 (Tyzzer, 1907), and before the early 1980s had rarely been recognized as a cause of human disease. In the early 1980s, *Pneumocystis carinii* pneumonia and other opportunistic infections began to emerge with the first cases of acquired immune deficiency syndrome (AIDS), and soon afterward, severe secretory diarrheal diseases were observed. Another protozoan, the tiny intracellular parasite, *Cryptosporidium*, was identified as the cause of these severe diarrheal diseases, which typically occurred in patients with severe immunodeficiency (CD4 count <50 cells/mm^3).

The pathogenicity of *Cryptosporidium* spp. in immunocompetent or moderately immunocompromised persons became particularly evident following the outbreak in Milwaukee, Wisconsin in 1993 during which approximately 403,000 people became ill with cryptosporidiosis through contamination of drinking water (MacKenzie et al., 1994; Kramer et al., 1996). This and other experience led to recognition of *Cryptosporidium* as a potentially life-threatening pathogen in persons with other causes of immunodeficiency or immunosuppression (e.g., X-linked immunodeficiency with hyper-immunoglobuline M caused by a defect in CD40 ligand (also termed CD154), chemosuppressive treatments associated with organ transplantion, cancer chemotherapy and severe malnutrition).

While the natural history of cryptosporidiosis remains somewhat poorly understood, infections caused by *Cryptosporidium* spp. are not limited to the small intestine. Using an immunosuppressed rat model experimentally infected with *Cryptosporidium parvum*, Roussel et al. showed in 1996 that the parasites could also be found in the biliary tract constituting a reservoir for future intestinal re-infections with the parasite. Patients with biliary tract involvement and profound immunodeficiency can present with acalculous cholecystitis, sclerosis cholangitis or pancreatitis in addition to severe diarrhea (Hashmey et al., 1997; Vakil et al., 1996; Teare et al., 1997). This condition is usually associated with markedly shortened survival.

In early 1993, the Division of AIDS, National Institute of Allergies and Infectious Diseases (NIAID), National Institutes of Health (NIH), responded to the situation in initiating a major search to identify existing drugs or compounds in development that may

[1] Dr. Rossignol was consultant, later expert in intestinal protozoan and helminthic infections for the Parasitic Diseases Programme at the World Health Organization in Geneva, Switzerland from 1981 to 1991.

E-mail address: jfross@stanford.edu

0014-4894/$ - see front matter © 2009 Published by Elsevier Inc.
doi:10.1016/j.exppara.2009.07.005

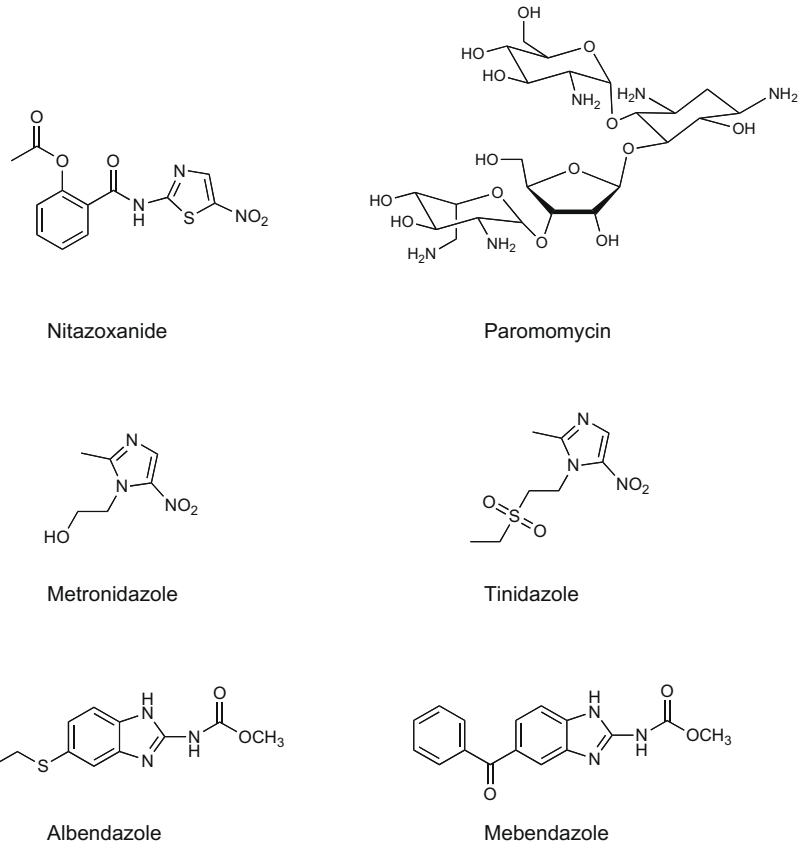

Fig. 1. Chemical structures of drugs used to treat *Cryptosporidium* or *Giardia*.

be active against *Cryptosporidium*. The screening was organized in the Saul Tzipori Laboratory at Tufts University School of Veterinary Medicine using a cell culture assay and several animal models of cryptosporidiosis including a piglet model, the only animal model in which *Cryptosporidium* causes diarrhea as in humans.

From the NIH effort, paromomycin and then nitazoxanide emerged as promising candidates for treating cryptosporidiosis. Ultimately, however, highly active antiretroviral therapy (HAART) proved to be the most effective therapy for reducing the frequency and severity of this disease in HIV-infected patients. Nitazoxanide was developed and licensed in the United States for treating cryptosporidiosis in non-immunodeficient children and adults, having demonstrated activity in reducing the duration of diarrhea and oocyst shedding in several double-blind, placebo-controlled clinical trials.

Today, cryptosporidiosis is recognized with increasing frequency as a cause of disease in the general population in outbreak and non-outbreak settings – perhaps due to greater awareness and improvements in diagnostic techniques (Yoder et al., 2008; Centers for Disease Control and Prevention, 2008; Mor et al., 2009). Outbreaks are almost exclusively associated with contamination of recreational or drinking water. In developing countries, cryptosporidiosis remains a serious threat as a frequent cause of malnutrition and death in young children.

3. Giardiasis

G. intestinalis (also known as *Giardia lamblia* or *Giardia duodenalis*) is both the most common intestinal parasite affecting humans in the United States and the most common cause of chronic diarrhea in travelers. Research into its epidemiology, pathogenesis, and treatment has intensified since *G. intestinalis* waterborne outbreaks were reported in Europe and the United States during the 1960s and 1970s (Craun, 1986; Farthing, 1992; Moore et al., 1969).

Giardia infects approximately 2% of the adults and 6% to 8% of the children in developed countries worldwide. It infects more than 40 animal species and is regarded as zoonotic by the World Health Organization (WHO) although animal reservoirs of human outbreaks have not yet been clearly identified. *Giardia* cysts can survive in water sources for several months in cold climates, and although the outbreaks have been linked to contaminated water (Marshall et al., 1997), the fecal-oral route is regarded as the major source of infection, particularly in countries where the water is warm or where there is little drainage and no reticulated water supply (Ortner et al., 1997). This is supported by the fact that giardiasis is prevalent in child care centers and in nursing homes (Nash and Weller, 1998; Cheney and Wong, 1993; Wittner and Tanowitz, 1992).

WHO in a press release in 1998, reported that 3 billion people live in unsewered environments in developing countries and the rate of giardiasis among them approaches 30%, suggesting that there are closer to 1 billion cases of giardiasis at any one time, contributing to 2.5 million deaths annually from diarrheal disease.

Historically, giardiasis has been somewhat neglected by tropical physicians much more concerned with amebiasis, schistosomiasis or the three main intestinal nematodes, *Ascaris*, the hookworms and *Trichuris*. The discovery that amebiasis caused by *Entamoeba histolytica*, the potentially invasive form of the disease, represented only a small proportion of the patients previously believed to be infected, has resulted in less emphasis on the importance *E. histolytica*. In fact, most people diagnosed with amebiasis were harboring *E. dispar*, a morphologically identical but non-pathogenic organism. The successes of praziquantel for schistosomiasis and the benzimidazole carbamates, mebendazole and albendazole