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Invited Review

Repurposing drugs for the treatment and control of helminth infections

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ABSTRACT

Helminth infections are responsible for a considerable public health burden, yet the current drug armamentarium is small. Given the high cost of drug discovery and development, the high failure rates and the long duration to develop novel treatments, drug repurposing circumvents these obstacles by finding new uses for compounds other than those they were initially intended to treat. In the present review, we summarize *in vivo* and clinical trial findings testing clinical candidates and marketed drugs against schistosomes, food-borne trematodes, soil-transmitted helminths, *Strongyloides stercoralis*, the major human filariases lymphatic filariasis and onchocerciasis, taeniasis, neurocysticercosis and echinococcosis. While expanding the applications of broad-spectrum or veterinary anthelmintics continues to fuel alternative treatment options, antimalarials, antibiotics, antiprotozoals and anticancer agents appear to be producing fruitful results as well. The trematodes and nematodes continue to be most investigated, while cestodal drug discovery will need to be accelerated. The most clinically advanced drug candidates include the artemisinins and mefloquine against schistosomiasis, tribendimidine against liver flukes, oxantel pamoate against trichuriasis, and doxycycline against filariasis. Preclinical studies indicate a handful of promising future candidates, and are beginning to elucidate the broad-spectrum activity of some currently used anthelmintics. Challenges and opportunities are further discussed.

Contents

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1. Introduction

Helminth infections caused by roundworms (nematodes) and flatworms (platyhelminths) comprise the greatest group of the neglected tropical diseases (NTDs) (Hotez et al., 2006). An estimated 11.5 million disability adjusted life years (DALYs) are attributed to intestinal nematode infections, schistosomiasis, lymphatic filariasis, onchocerciasis, food-borne trematodiasis, cysticercosis and echinococcosis (Murray et al., 2012). Most of the burden of these diseases results from disability (rather than premature death), influencing school attendance, child development and overall economic productivity, thus resulting in disease driven poverty traps (Hotez et al., 2006). In a recent special issue of the Disease Clinics of North America (Zumla and Keiser, 2012), cestode infestations (Brunetti and White, 2012), schistosomiasis (Gryseels, 2012), food-borne trematodiases (Fürst et al., 2012), filariases (Knopp et al., 2012a) and soil-transmitted helminthiases (Knopp et al., 2012b) were presented in great detail and hence for background information on these diseases, the reader is referred to these excellent publications.

Preventive chemotherapy is the strategy of choice to control schistosomiasis, soil-transmitted helminthiases, lymphatic filariasis, onchocerciasis and food-borne trematodiases yet as emphasized in the following sections of this review, limited tools are available to treat these infections. In addition, for many of the available drugs, resistance is a threat since it has already developed in veterinary medicine and many of the drugs have an imperfect activity profile. Yet clear targets have been set to eliminate and control several of these diseases (http://www.unitingtocombatntds.org/downloads/press/london_declaration_on_ntds.pdf). Hence research and development (R&D) to find the next generation of anthelmintics is indispensable. However, a recent systematic assessment of databases of drug regulatory authorities and the World Health Organization (WHO) as well as clinical trial registries revealed a dry drug pipeline for NTDs, supported by the fact that no new chemical entity had been approved for these diseases in the past decade (Pedrique et al., 2013).

Drug repurposing (also termed re-profiling, re-tasking, therapeutic switching or drug repositioning) is the process of developing new indications for existing, failed or abandoned drugs or advanced clinical candidates (Sekhon, 2013). Drug repurposing is a useful strategy to accelerate the drug development process due to lower costs, reduced risk and decreased time to market due to availability of preclinical data (Padhy and Gupta, 2011). This enables not only pharmaceutical companies but also public-sector researchers to engage in drug discovery and development efforts (O'Connor and Roth, 2005), and hence might result in treatment options for diseases almost exclusively addressed by public sector researchers, such as the neglected tropical diseases. Over the past years, a variety of drug-repurposing initiatives have been launched with particular attention to neglected tropical and rare diseases (Allarakhia, 2013), hence it is likely that these efforts will bear fruit in the next years.

The aim of the present article is to highlight the status of drug repurposing for neglected helminth diseases. The focus is on the state-of-the-art treatments and how drug repurposing has been supplying the drug development pipeline for schistosomiasis, infections with major food-borne trematodes, *Fasciola* spp., *Opisthorchis* spp. and *Clonorchis sinensis*, soil-transmitted helminthiasis, *Strongyloides stercoralis*, the major human filariasis, lymphatic filariasis and onchocerciasis, taeniasis, neurocysticercosis and echinococcosis.

Our review complements a recent article by Andrews and colleagues which summarized antiprotozoal drug repurposing for major parasitic protozoal diseases including malaria, trypanosomiasis, and leishmaniasis (Andrews et al., 2014).

2. Schistosomiasis and food-borne trematodiases

2.1. Current treatment

Since its discovery in the 1970s, praziquantel has replaced many other drugs as the sole treatment for a range of helmintic infections. Praziquantel is effective against all three major species of *Schistosoma* (*S. mansoni*, *S. haematobium* and *S. japonicum*), and is the standard treatment against *C. sinensis*, *Opisthorchis viverrini* and *Opisthorchis felineus*, and intestinal flukes (Keiser and Utzinger, 2004; Utzinger and Keiser, 2004). It is administered orally, is safe, and highly effective.

As mentioned above, preventive chemotherapy is the strategy of choice to control schistosomiasis (WHO, 2006). This program is expected to expand ten-fold to include the treatment of 235 million people by 2018 (Knopp et al., 2013) which, on the one hand may significantly drive down morbidity and transmission but, on the other hand, would exacerbate drug pressure, likely resulting in resistance to praziquantel (Caffrey, 2007). Furthermore, praziquantel still has deficiencies: it is inactive against the juvenile stage of *Schistosoma* spp. and its (S)-enantiomer is inactive, a problem because at the moment, it is not separated from the (R)-enantiomer in production and hence the tablets are large and bitter (Stothard et al., 2013). Therefore, there is great motivation to seek alternative medications.

In the case of fascioliasis, triclabendazole is the treatment of choice (Keiser et al., 2005). Triclabendazole is safe and effective against both the human and veterinary forms of the disease. However, there are two major setbacks: in veterinary medicine, triclabendazole resistance has already been documented (Brennan et al., 2007). Additionally, triclabendazole is not registered for use in many nations, and is therefore not always available for the treatment of human fascioliasis (Keiser et al., 2005).

2.2. Repurposed drugs

2.2.1. Antimalarials and their derivatives

The largest anthelmintic drug repurposing success story by far has been the application of antimalarials against a wide variety of trematode infections, as well as other broader applications.