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Commentary

An old drug as a promising new cure for the hard-to-treat echinococcosis

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The zoonotic echinococcosis afflicts humans in two forms: cystic echinococcosis (**CE**; aka hydatidosis) and alveolar echinococcosis (**AE**), which are caused by tapeworms *Echinococcus granulosus* and *E. multilocularis*, respectively [1]. Dogs, foxes and other carnivores are the definitive hosts, in which the mature tapeworms in their intestines produce eggs that are released into the environment. Eggs ingested by intermediate hosts (e.g., sheep, cattle, pig and camel) hatch in the intestine to release oncospheres that migrate through the portal and lymphatic vessels to the liver (main infection site) or other organs (e.g., lungs, brain, spleen and bones), where they develop into metacestodes (hydatid cysts). Humans are accidental intermediate hosts. When cysts are ingested by a definitive host, protoscoleces produced by metacestodes evaginate their scoleces that attach to the intestinal walls and develop into egg-producing adult worms [1].

Among the two forms of echinococcosis, **CE** is much more prevalent and remains highly endemic in western China, Central Asia, South America, Mediterranean and eastern Africa. **AE** is only endemic in northern hemisphere, mainly in some regions of China, the Russian Federation and some countries in Europe and North America. The hardest-hit regions are the western China and Central Asia that are highly endemic for both **CE** and **AE** and accounts for 90% or more of the estimated global AE cases [1, 2]. Clinically, echinococcosis causes damage or dysfunction of targeted organs, mainly the liver (70% for **CE** and virtually 100% for **AE**), lung (20% for **CE**) and other organs (brain, spleen, kidney and heart; ~10% for **CE**).

Because early stages of *Echinococcus* infections are typically asymptomatic, most patients seeking medical care are in the late stages of **CE** or **AE**. Treatments are usually difficult with limited options [1], which include long-term chemotherapy, or chemotherapy combined with puncture-aspiration-injection-reaspiration (**PAIR**) or surgery for **CE**, depending on the lesion size and stage of **CE**; or various surgery procedures combined with multi-year chemotherapy for **AE**. Currently, albendazole (**ABZ**) is the standard anti-echinococcosis medicine, while an analog mebendazole (**MBZ**) may be used as an alternative for patients experiencing severe adverse effects with **ABZ** [1, 3, 4]. However, **ABZ** has limit efficacy against echinococcosis. For example, an earlier retrospective study revealed that the recovery rates with **ABZ** treatment only ranged from 11.8% to 35.2% in **CE** cases, and 40% cases did not respond favorably [5]. Moreover, some patients may be intolerant to **ABZ/MBZ**, and drug resistance to benzimidazoles are also common in helminths. Therefore, there is a keen desire to develop new and improved anti-echinococcosis drugs.

In an article in *EBioMedicine* [6], Li and colleagues report a novel anti-*E. granulosus* activity of pyronaridine both in vitro and in vivo. Pyronaridine showed low micromolar protoscolicidal activity in vitro ($\mathbf{EC_{50}}$ = 49.0 μM), which was slightly better than **ABZ** ($\mathbf{EC_{50}}$ = 79.2 μM). In mouse infection model, pyronaridine impressively killed 100% of the cysts by intraperitoneal injection at 57 mg/kg/d for 3 days. When administrated orally at 57 mg/kg/d for 30 days, pyronaridine produced 90.7% cyst mortality, which is much more efficacious than **ABZ** (22.2% cyst mortality at 50 mg/kg/d).

Based on body surface area normalization to convert drug dosage from animal studies to humans [7], a dose of 57 mg/kg in mice is equivalent to a dose of 4.5 – 5.0 mg/kg/d in human adults (or 270 – 300 mg per 60 kg adult), which is 3 times lower than the average dose of **ABZ** at 15 mg/kg/d (or 900 mg per 60 kg adult) for treating human echinococcosis. For comparison, the oral dose of pyronaridine used to treat malaria in China is 24 mg/kg/d [8]. Pyronaridine is an antimalarial drug approved for use in China since 1980s and a component of the artemisinin combination therapy pyronaridine/artesunate (Pyramax) approved by European Medicines Agency (EMA) in 2016 [8]. Therefore, pyronaridine's preclinical and some clinical properties (e.g., pharmacokinetics and toxicity profile) are well characterized and in a good position for quickly entering clinical trials.

In China and other countries where pyronaridine is an approved medicine, patients with echinococcosis might potentially benefit earlier from "off-label" prescription of pyronaridine, particularly for those with severe adverse effects or resistance to the treatment with **ABZ/MBZ**. In addition to advancing the study to clinical trials, it is also worth to evaluate the deworming activity of pyronaridine in dogs and other definitive hosts, which is critical in breaking the transmission cycle for both **CE** and **AE**.

In addition to antimalarial and anti-echinococcosis activity, pyronaridine has be found to also possess activities against Ebola virus [9]. However, the mechanism and mode of action of pyronaridine is not fully understood. DNA topoisomerases have been implied as the drug target in antimalarial and anti-echinococcosis activity [6, 8], but the evidence is not fully compelling. The recent advancement in

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biotechnology such as pharmacogenomics, proteomics and metabolomics may provide an opportunity to reveal the mechanism of action of pyronaridine against malaria and echinococcosis.

Declaration of Competing Interest

The authors declare no conflict of interests.

Authors' contributions

GZ and ML discussed the major points to be presented in this commentary; GZ drafted the manuscript; GZ and ML finalized the manuscript.

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