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Acting beyond 2020: better characterization of praziquantel and promising antischistosomal leads

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The commitment to eliminate schistosomiasis as a public health problem has mobilized the expansion of praziquantel treatment to meet the London Declaration targets. New research has thus sought to elucidate praziquantel's safety and efficacy in key demographics such as preschoolers and pregnant women, as well as novel elements of its pharmacokinetics and pharmacodynamics. At the same time, reliance on praziquantel *ad infinitum* would place schistosomiasis control at risk, should resistance occur. In response, the academic community has been filling the preclinical drug discovery pipeline with novel or resurrected drug candidates against schistosomiasis. In this review, we highlight the latest research on praziquantel treatment dynamics, which aims to improve the utility of this important drug. Moreover, we present the most promising preclinical antischistosomal candidates, which should be studied further to achieve the ultimate goal- an alternative antischistosomal drug in the near future.

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Introduction

The London Declaration target to control morbidity due to schistosomiasis by 2020 and eliminate it as a public health problem by 2025 has been matched by a promise from Merck KGaA to increase praziquantel coverage by 10-fold to 250 million tablets per year [1]. The importance of this development cannot be understated, as current treatment coverage continues to lag at just over 20% [2]. Nonetheless, important knowledge gaps about this old drug must be closed if we are to truly achieve sufficient treatment coverage [3]. Particularly, the safety, and efficacy of praziquantel in vulnerable populations that have not been included in mass drug administration (MDA) campaigns are important missing pieces.

Expanding treatment coverage is also a double-edged sword for a disease that has only one treatment: on the one hand, it is certainly necessary if the goal of elimination is to be achieved and, on the other hand, the increased drug pressure raises the risk of resistance to praziquantel [4,5]. The scientific community has thus called for and made considerable efforts to fill the antischistosomal pipeline with new candidates [6,7].

In this review, we summarize the most recent research on praziquantel efficacy in important demographics, as well as novel findings on its pharmacodynamics. We also spotlight the most promising preclinical lead candidates. We will not list all compounds that have been tested *in vivo*, as this has been thoroughly inventoried by two recent reviews [8••,9]. Rather, we place an emphasis on compounds that have shown potent *in vivo* efficacy (>70% worm burden reduction) after oral, single dose administration, from classes that have been well researched, and thus have the most potential to move forward on the drug development pipeline.

Praziquantel: from pharmacokinetic to metabonomic studies

An often overlooked but important demographic is pregnant women with schistosomiasis. For over a decade, the World Health Organization (WHO) has recommended treating infected pregnant women, but a lack of robust safety and efficacy studies have discouraged adherence to this policy [9]. Since this recommendation in 2006, two randomized controlled trials on the use of praziquantel during pregnancy have been conducted, which confirmed that praziquantel is safe to administer to pregnant women: that is, only transient adverse events were reported, similar to those in non-pregnant women, and no effect on fetal or neonatal health was observed [10,11]. Moreover, preliminary data on the pharmacokinetics of praziquantel in pregnant women showed that it is not significantly altered by pregnancy [12••].

The recognition that preschool aged children are affected by schistosomiasis and should be treated has prompted safety and efficacy studies of praziquantel in this demographic [13]. As inconsistency in study methodologies complicated optimal dose determination, two dose-finding studies (investigating doses of 20, 40 and 60 mg/kg) in preschool aged children infected with *S. mansoni* or

S. haematobium were recently conducted. Over the dose range tested, praziquantel displayed highest responses with 20 mg/kg and 40 mg/kg in preschoolers infected with *S. haematobium* and *S. mansoni*, respectively. The authors therefore supported the use of the WHO-recommended dose of 40 mg/kg also for this age group [14••,15].

Complementary pharmacokinetic (PK) studies from these clinical trials revealed an association between exposure to R-praziquantel (area under the curve (AUC) and maximum serum concentration (C_{max})) and probability of cure, based on noncompartmental modelling [16]. On the other hand, studies in mice hinted that rather R-praziquantel concentrations in the mesenteric veins (where adult *S. mansoni* reside, before first pass metabolism) are responsible for efficacy against *S. mansoni* [17]. Both studies confirm recent *in vivo* and *in vitro* elucidations of R-praziquantel as the main effector enantiomer [18,19]. S-praziquantel activity was, however, not insignificant against *S. haematobium in vivo* and although its ED_{50} was five-fold higher than that of R-praziquantel, plasma concentrations of S-praziquantel are also higher [19]. Indeed, both S-praziquantel and total AUC were found to be associated with increased cure rates in Ugandan children, though the authors noted limitations in measuring the R-enantiomer [20].These somewhat contradictory PK and efficacy results therefore stress the need for population pharmacokinetic modelling studies, which are now underway, in order to better understand the PK/PD behaviour of this drug to inform decision making [21]. The current development of a much-needed pediatric form of praziquantel aims to overcome its child-unfriendly elements (overwhelmingly bitter, very bulky) by eliminating the S-enantiomer from the racemic tablet [21].

As gut microbial composition may affect drug absorption, a small subset of stool samples from the dose-finding *S. mansoni* praziquantel trial were analyzed [22•]. Children who were cured after praziquantel treatment were found to harbor a higher abundance of *Fusobacterium* spp. before and 24 hours after treatment than those that were not cured, suggesting a potential role of gut microbiota in treatment success. A heavy *S. mansoni* infection itself was found to alter microbial composition, marked by an overabundance of *Klebsiella* genus and *Enterobacter arachidis* bacteria. Complementary metabonomic studies from the same trial revealed that both a heavy infection as well as praziquantel intake trigger biochemical effects primarily associated with gut microbial, gut and liver metabolism, which partly reflected earlier findings in adults with a heavy *S. mansoni* burden [23,24]. Further studies with larger patient populations and cohorts would help clarify the role of microbiota in praziquantel efficacy.

Potential alternatives to praziquantel

Artemisinin-inspired ozonides

An active source of novel antischistosomal candidates continues to be antimalarials and their derivatives, as the heme detoxification pathway common to both *Plasmodium* spp. and *Schistosoma* spp., is posited to be an excellent and likely drug target [25,26]. Especially the artemisinins have shown efficacy against *Schistosoma* spp., from *in vitro* studies to clinical trials, though they are more active against juvenile worms than against adult-stage infections [27]. The synthetic ozonides incorporate the active endoperoxide pharmacophore, while optimizing pharmacokinetic and safety parameters. In addition to advanced research as potential antimalarials, the ozonide's antischistosomal activity has also been extensively probed [28,29]. Initial tests in *S. mansoni*-infection models presented the ozonides OZ78, OZ277, OZ288, OZ165 and OZ418 as reducing juvenile worm burdens by at least 80%, but with more variable activity against adult infections in different rodent models [29–31]. Importantly, OZ78 and OZ418 have demonstrated high *in vivo* activity against all 3 major human schistosome species, against both the juvenile and adult stages [29,31–34]. In infected rodent pharmacokinetic studies, OZ418 plasma levels remained above the compound's *in vitro* IC_{50} value of 27.4 μg/ml (against adult *S. mansoni*) for at least 75 hours. The compound also proved to be stable in plasma and was only weakly affected by cytochrome P450 metabolism [35•]. OZ418 is therefore an excellent lead candidate for which the mechanism of action is, however, yet to be elucidated (Figure 1, Table 1).

Rescuing old candidates

As praziquantel was adopted for preventative chemotherapy campaigns, commercial drug discovery efforts were subsequently dropped [36]. However, two promising preclinical candidates that were being explored at Hoffman-LaRoche were resurfaced and investigated.

Ro 13-3978 (Figure 1), an aryl hyadontoin with structural similarity to an old antischistosomal, niridazole), has shown superior efficacy in an adult *S. mansoni*-mouse infection, with an ED_{50} of 14.6 mg/kg compared to 172–202 mg/kg ED_{50} for praziquantel. Moreover, whereas praziquantel has no effect against juvenile stage worms, Ro 13-3978 presented an ED_{50} of 138.9 mg/kg (Table 1). The activity of Ro 13-3978 appears to be schistosome specific, with activity against all major schistosome species, as no efficacy was observed in *in vivo* studies against related trematodes, *Fasciola hepatica* and *Echinostoma caproni* [37,38]. The drug has an interesting mode of action as it is not active *in vitro* and not metabolized, yet exhibits fast activity *in vivo* [37]. Immunohistochemical studies after treatment with Ro 13-3978 revealed potential assistance from host macrophages in worm clearance, however, the full mode of action remains to be elucidated [39]. Structure–activity relationship studies have yielded a handful of analogues with consistently high (>90%) WBR at an oral dose of 100 mg/kg [40,41]. Pharmacokinetic studies, as well as testing against