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Positive Action

Despite affecting millions of people across the globe, treatment options for schistosomiasis in very young children have thus far remained limited. However, a recent collaboration hopes to develop solutions that are widely available and affordable, as well as easily adoptable

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Known since ancient times, schistosomiasis – also called bilharzia – is one of the most prevalent parasitic diseases in tropical and subtropical countries, yet it is often neglected. It is a severe, chronic inflammatory disease caused by flatworms, commonly associated with conditions of poverty such as lack of sanitation, clean water and unhygienic behaviour. The disease is endemic in 78 countries: some 800 million people are at risk and an estimated 240 million people are infected, with more than 90% of them living in Africa.

There are two major forms of schistosomiasis – intestinal and urogenital – caused by six species of blood fluke (1). Urogenital schistosomiasis is also considered to be a risk factor for HIV infection, especially in women (2). The disease principally affects people living in rural agricultural and peri-urban areas – of the infected patients, about 20 million suffer severe consequences from the disease (3), and anything from 10,000-280,000 deaths are related. In many areas, schistosomiasis infects a large proportion of children under the age of 14 years (4-9).

Treatment Issues

The recommended global strategy to control schistosomiasis is preventive chemotherapy that involves the periodic administration of the antischistosomal drug praziquantel (PZQ) to entire at-risk populations without prior diagnosis. PZQ tablets (usually 600mg) are administered at single oral doses of 40-60mg per kilogram of body weight. This standard recommended treatment is available for adults and school-aged children. However, a paediatric formulation suitable for treating preschool-aged

children is lacking, despite this sub-population representing a high-risk group for schistosome infections, and counting for 10-20 million of the global prevalence. The preschool age group must be addressed if we are to move towards elimination of the disease (4).

The need to treat preschool-aged children is now widely acknowledged (4-12). Not only do they play a role in local disease transmission but, importantly, active infections acquired at early ages might aggravate the clinical significance of schistosomiasis in later life (13). A new strategy is needed not only in the context of mass drug administration, but also for specific disease case management upon confirmation of diagnosis in young children. The available PZQ 600mg tablets cannot be readily administered to this age group.

Fighting Infection

Praziquantel is the gold standard treatment for schistosomiasis in adults and school-aged children. The Pediatric Praziquantel Consortium is making progress towards developing an effective treatment for children as young as three months.

The current drug is a 1:1 mixture (racemate) of the biologically active levo-praziquantel (L-PZQ) enantiomer and the inactive dextro-praziquantel enantiomer (14). This mixture has a bitter taste, which can lead to gagging or vomiting if tablets are chewed, and the tablet cannot be taken intact due to the risks associated with accidental choking in children aged less than six years. Although crushing of PZQ tablets has been employed in recent studies with preschool-aged children infected with schistosomes (9,10, 15-17), there is no reliable information on the bioavailability of crushed tablets, or on whether or not this approach provides optimal efficacy and safety. In addition, it is difficult to mask the bitter taste of crushed tablets. Infants and children react unfavourably to bitter tastes, and the more bitter the drug, the more likely it will be rejected (18,19). This leads to compliance problems and issues of under-dosing.

United Approach

Figure 1: A pair of Schistosoma haematobium blood worms

To address the existing treatment gap, the non-profit Pediatric Praziquantel Consortium has been set up. The consortium's sole goal is to develop a suitable PZQ formulation that can be readily administered to the paediatric group aged three months to six years; and unlike many public-private partnerships in the area of tropical diseases, it does not run a portfolio of various products that can act as substitutes for the time being. Acceptable palatability, proven efficacy and safety of the new formulation are priorities, and key characteristics of the paediatric medication also include an appropriate shelf-life to withstand the challenging field temperatures, extreme humidity conditions and complex logistics that prevail in Africa.

Within this consortium of highly driven partners, Merck is responsible for leading the programme and providing the necessary chemistry and manufacturing expertise, resources and support relating to praziquantel. In addition, it provides the preclinical, clinical and regulatory resources needed to execute the project efficiently and successfully. Astellas has developed the paediatric formulations and provides its expertise in clinical development in children, pharmacokinetic modelling and health access. Swiss TPH brings extensive experience in helminths biological and pharmacological research, epidemiology and clinical research on drug effectiveness and efficacy in endemic regions, while Farmanguinhos – the federal governmental pharmaceutical laboratory of the Fiocruz Foundation in Brazil – supports the manufacturing activities and offers unique expertise in producing and supplying the new paediatric formulation products in endemic countries. Simcyp, a small UK research-based company, will build and validate a pharmacokinetic model that will allow for a better prediction of appropriate dosage for use in the paediatric clinical trials.

The consortium is steered by a clear governance structure, outlined in a consortium agreement signed by all the partners, and is run by an experienced team of top scientists and high-level executives. Governance is facilitated by TI Pharma, a non-profit organisation and independent party with an extensive portfolio of international public-private partnerships in drug research and development, including in the area of neglected diseases. Finally, a scientific advisory panel of renowned international experts in schistosomiasis, paediatrics and other relevant disciplines regularly helps the consortium to overcome the many scientific, regulatory and access challenges that are typical during neglected tropical disease drug development. The consortium is supported by grant contributions, awarded by the Bill and Melinda Gates Foundation in 2013, and by the Global Health Innovative Technology Fund in 2014.

In order to maximise the chances of successful delivery of this drug to the children in need, the consortium team is currently working on two projects in parallel: the development of a paediatric formulation containing the racemate PZQ (rac-PZQ) drug substance, and one

containing the L-PZQ pure enantiomer. The choice to proceed with one formulation or the other will take place after evaluation of the results from the first clinical studies (expected summer 2015).

Plan of Action

The consortium has recently successfully completed the preclinical phase of the programme. During this stage, several paediatric formulation candidates have been developed and initial orally disintegrating tablet (ODT) formulations have been selected. ODTs are suitable for use in young children as they can either be given to children over two years of age by direct administration into the mouth, or they can be dispersed in a small amount of water and given as a suspension to infants and toddlers below two years. Taste masking is currently achieved by using slightly sweet fillers and a sweetener.

The technology for manufacturing these candidate formulations has been transferred from Astellas to Farmanguinhos and Merck Serono for the rac-PZQ ODTs and the L-PZQ ODTs, respectively. The formulation composition and manufacturing conditions have been optimised at the receiving sites, and production campaigns of the drug material to supply the first clinical studies have been completed.

In addition, the team has generated the necessary non-clinical drug metabolism and pharmacokinetics, Good Laboratory Practice toxicology, and safety pharmacology data to enable the start of Phase 1 clinical trials.

The clinical programme, which will be conducted in schistosomiasis-endemic countries, began towards the end of 2014 and, if successful, will form the basis of a regulatory submission. The first studies consist of two relative bioavailability studies in healthy adult volunteers, designed to evaluate the benefit/risk ratio of the new formulations and confirm the dose for the subsequent paediatric clinical trial. A swill and spit taste study in children is planned in Tanzania in 2015 to compare the palatability of the L-PZQ ODTs, the rac-PZQ ODTs and the commercial PZQ 600mg tablets.

Appropriately designed paediatric efficacy and safety studies, guided by physiologically-based pharmacokinetic modelling, will be subsequently conducted in endemic countries yet to be defined. Results of a recently conducted meta-analysis on the efficacy and safety of PZQ in children will also be used to guide the design of future clinical studies (20).

Set for Success?

The consortium's goal is to register and launch the new paediatric formulation in endemic countries – in South America (including Brazil) and in sub-Saharan Africa. Due to the complex and challenging regulatory environment that prevails in sub-Saharan Africa (21), the consortium team has started to interact closely with the African endemic countries' regulators and the World Health Organization (WHO).

In addition, during development, the consortium will address three important elements of future market access for the new paediatric formulation. The first is availability, including the logistics of making the new ODTs (plus local manufacturing), ordering, shipping, storage, distribution, and delivery of the new formulation in order to ensure it reaches users. The second is affordability, including pricing of ODTs, taking into account the individual patient's ability to pay, as well as the resources of governments and other funders. The third is adoption, counting the new formulation's future recommendation by the WHO, and its acceptance by local policy-makers, patients and healthcare providers in the endemic countries.

Achievements to date

- Several new PZQ ODT formulation candidates developed
- Successful completion of preclinical studies
- First clinical trial drug supplies available
- Phase 1 clinical trials started
- Close to $3 million external funding raised

References

1. Parasite species and geographical distribution of Schistosomiasis, WHO Fact Sheet 115, February 2014. Visit: www.who.int/mediacentre/factsheets/fs115/en
2. Feldmeier H, Krantz I and Poggensee G, Female genital schistosomiasis as a risk-factor for the transmission of HIV, *Int J STD AIDS* 5(5): pp368-372, 1994
3. Kheir MM *et al*, Mortality due to schistosomiasis mansoni: A field study in Sudan, *Am J Trop Med Hyg* 60(2): pp307-310, 1999

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4. Sousa-Figueiredo JC, Martha Betson M and Russell Stothard J, Treatment of schistosomiasis in African infants and preschool-aged children: Downward extension and biometric optimization of the current praziquantel dose pole, *International Health* 4: pp95-102, 2012
5. Stothard JR *et al*, Schistosomiasis in African infants and preschool children: Let them now be treated! *Trends in Parasitology* 29(4): pp197-205, 2013
6. Mafiana CF, Ekpo UF and Ojo DA, Urinary schistosomiasis in preschool children in settlements around Oyan Reservoir in Ogun State, Nigeria: Implications for control, *Trop Med Int Health* 8(1): pp78-82, 2003
7. Opara N *et al*, Genitourinary schistosomiasis among pre-primary schoolchildren in a rural community within the Cross River Basin, Nigeria, *J Helminthol* 81: pp393-397, 2007
8. Bosompem KM *et al*, Infant schistosomiasis in Ghana: A survey in an irrigation community, *Trop Med Int Health* 9(8): pp917-922, 2004
9. Odogwu SE *et al*, Schistosoma mansoni in infants (aged <3 years) along the Ugandan shoreline of Lake Victoria, *Ann Trop Med Parasitol* 100: pp315-326, 2006
10. Garba A, Barkir'e N and Djibo A, Schistosomiasis in infants and preschool-aged children: Infection in a single Schistosoma haematobium and a mixed S. haematobium-S. mansoni foci of Niger, *Acta Tropica* 115(3): pp212-219, 2010
11. Ekpo UF *et al*, Urinary schistosomiasis among preschool children in a rural community near Abeokuta, Nigeria, *Parasites and Vectors* 3(1): p58, 2010
12. WHO, Report of a meeting to review the results of studies on the treatment of schistosomiasis in preschool-age children, 2011. Visit: http://whqlibdoc.who.int/publications/2011/9789241501880_eng.pdf
13. Stothard J R *et al*, Schistosoma mansoni infections in young children: When are schistosome antigens in urine, eggs in stool and antibodies to eggs first detectable? *PLOS Neglected Tropical Diseases* 5(1): e938, 2011
14. Meister I *et al*, Activity of praziquantel enantiomers and main metabolites against Schistosoma mansoni, *Antimicrob Agents Chemother* 58(9): pp5,466-5,472, 2014
15. Betson M *et al*, Intestinal schistosomiasis in mothers and young children in Uganda: Investigation of field-applicable markers of bowel morbidity, *American Journal of Tropical Medicine and Hygiene* 83(5): pp1,048-1,055, 2010
16. Sousa-Figueiredo JC *et al*, Performance and safety of praziquantel for treatment of intestinal schistosomiasis in infants and preschool children, *PLOS Neglected Tropical Diseases* 6(10): pp1-9, 2012
17. Navaratnam AMD *et al*, Efficacy of praziquantel syrup versus crushed praziquantel tablets in the treatment of intestinal schistosomiasis in Ugandan preschool children, with observation on compliance and safety, *Trans R Soc Trop Med Hyg* 106(7): pp400-407, 2012
18. Mennella JA and Beauchamp GK, Optimizing oral medications for children, *Clinical Therapy* 30(11): pp2,120-2,132, 2008
19. Schwartz C *et al*, Developmental changes in the acceptance of the five basic tastes in the first year of life, *British Journal of Nutrition* 102(9): pp1,375-1,385, 2009
20. Zwang J and Olliaro P, Clinical efficacy and tolerability of praziquantel for intestinal and urinary schistosomiasis, a meta-analysis of comparative and non-comparative clinical trials, *PLOS Neglected Tropical Diseases* 8(11): e3286, 2014
21. Drugs for Neglected Diseases Initiative Meeting Report (November 2013), *The Road to Regulatory Harmonization for Africa: Accelerating Access to Essential Medicines and Vaccines*, Nairobi, Kenya, 4 June 2013

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