Rapid induction of clinical tolerance in a placebo-controlled clinical trial investigating repeated controlled exposure to *Schistosoma mansoni*

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Epidemiological data from endemic settings suggests that (partial) immunity to schistosomiasis develops over time, and is likely enhanced by repeated infections and treatments leading to enhanced or prolonged antigen exposure. Moreover, animal studies have demonstrated that protection can be achieved after repeated immunisation with irradiated cercariae. In this study, we aimed to investigate the protective efficacy and safety of consecutive exposure-treatment cycles with *Schistosoma mansoni* (*Sm*) in healthy, schistosome-naïve participants using the single-sex controlled human *Sm* infection model. We enrolled 24 participants who were randomised (1:1) to either three (reinfection) or one (infection control) exposures to 20 male cercariae. The infection control group received two mock exposures first. Treatment with praziquantel (or placebo for infection controls) was given 8 weeks after the first and second (mock) exposure. All participants were treated with praziquantel 12 weeks after the third exposure. Throughout the study, adverse events were collected as well as serum to measure circulating anodic antigen (CAA) secreted by juvenile and adult worms to determine infection status. All but one participant completed follow-up. The percentage of participants with detectable infection after the final exposure (CAA ≥ 1.0 pg/mL) in the reinfection group was 82% (9/11) and 92% (11/12) in the infection control group. In the reinfection group, more related adverse events were reported after the first infection (45%) as compared to the second (27%) and third infection (28%). Severe acute schistosomiasis (AS) was observed in both groups after the first infection (2 out of 12 in reinfection group and 2 out of 12 in infection control group), but no AS was reported after the subsequent infections. In conclusion, repeated *Sm* infection led to clinical tolerance, but did not result in (sterile) protection. Further investigation into the underlying immune response will result in better understanding of immunity to schistosomes.