

EDITORIAL COMMENT

A New Epoch in Antitrypanosomal Treatment for Chagas Disease*



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For clinicians who treat adults with chronic Chagas disease, the last several years have brought great optimism and equally great frustration. For the first time in 40 years, new drug candidates are being tested in rigorous clinical trials for efficacy against chronic long-standing *Trypanosoma cruzi* infection (NCT01377480, NCT01489228) (1-3). These recent trials have confirmed that quantitative polymerase chain reaction (qPCR) is an excellent early marker for treatment failure and that benznidazole therapy results in sustained clearance of parasites from the peripheral blood. That's the good news. The bad news is that none of the new compounds has come close to benznidazole in efficacy. And the worst news is that benznidazole showed no significant efficacy to prevent progression of established Chagas cardiomyopathy in a large double-blinded, randomized, placebo-controlled trial that took more than 10 years to complete (Benznidazole Evaluation for Interrupting Trypanosomiasis [BENEFIT]; NCT00123916) (4).

Benznidazole and nifurtimox have been known since their introduction in the early 1970s to have high efficacy in the acute phase of Chagas disease, which corresponds to the 2 to 3 months after initial infection (5). Their efficacy in the chronic phase has been the subject of heated and ongoing debate (6,7). In the late 1990s, treatment of children with chronic *T. cruzi* infection (early chronic phase, presumed infected <15 years using age as a proxy) became the

standard of care, due to placebo-controlled trials of benznidazole that showed approximately 60% cure on the basis of conversion to negative serology 3 to 4 years after treatment (8,9). Nonrandomized data published in 2006 suggested that treatment of adults could significantly decrease progression of Chagas cardiomyopathy (10), leading to recommendations that antitrypanosomal therapy should generally be offered to infected adults up to 50 years of age (11). These findings have seemingly been contradicted by the results of the BENEFIT trial, but the study group patients differed substantially. The nonrandomized study subjects had a mean age of 39 years and two-thirds had normal cardiac function at baseline (10). In contrast, the BENEFIT trial study patients had a mean age of 55 years, all had cardiac damage on the basis of electrocardiographic abnormalities, and nearly one-half had decreased ejection fraction at baseline, indicating ventricular dysfunction (4). The question of whether treatment provides clinical benefit for those with no or very early cardiac signs therefore remains unanswered (12).

SEE PAGE 939

The first drugs to be tested in recent trials were posaconazole and related azole compounds, on the basis of promising animal data and a known safety record in humans (13,14). The Phase II trial by Morillo et al. (3) published in this issue of the *Journal* tested posaconazole compared with benznidazole and the combination of the 2 drugs. We now know that 80% to 90% of those treated with posaconazole return to detectable parasitemia by 12 months post-treatment, compared with benznidazole failure rates of 6% (per protocol) to 38% (intention-to-treat) (2). At the time the current trial was designed, treatment failure rates by qPCR were unknown for both drugs, and the

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investigators assumed a benznidazole failure rate of 90%. In addition, the power calculations were on the basis of the benznidazole versus posaconazole comparison alone (3). Thus, the trial was not adequately powered to detect a difference in failure rates between the benznidazole and combination arms. Given the low failure rates in the arms that included benznidazole, impractically large sample sizes would have been required.

The important question, not answered by this trial, is whether adding a second drug can achieve high efficacy while allowing a substantial reduction in benznidazole dosage and adverse effects. In the first posaconazole trial, benznidazole failure rates differed markedly between the per-protocol and intention-to-treat analyses because of early treatment withdrawal in one-fifth of benznidazole-treated patients (2). Among those who completed the 60-day course, 94% had negative qPCR results throughout the follow-up period. In the current trial, the rate of benznidazole discontinuation was even higher, probably because the dose was higher (400 mg/day vs. 300 mg/day), leading to a higher rate of adverse effects. Nevertheless, the benznidazole-containing arms of the trial showed $\geq 80\%$ sustained parasite clearance, even in the intention-to-treat analysis. The median time to benznidazole discontinuation was 40 days. Together with preliminary data on intermittent regimens (15), these results suggest that

a lower total dose of benznidazole monotherapy might achieve high efficacy while decreasing the rate of adverse effects. Combination regimens may allow an even greater reduction in dosage, with the added advantage of minimizing the possibility of acquired drug resistance.

Development of new regimens for chronic *T. cruzi* infection remains challenging. Animal models fail to accurately predict efficacy in humans, and most new drug candidates share the same mechanism of action (16,17). Although qPCR is now accepted as a reliable early indicator of treatment failure, tissue parasites may remain, despite negative peripheral blood PCR, and we still lack a timely test of cure for use in humans (18). New candidate screening protocols that search for drugs with novel targets and mechanisms (19), and animal models that allow dynamic in vivo visualization of tissue parasite loads (20), have the potential to accelerate drug development as never before. Let us hope that the next 5 years bring more optimism and less frustration to Chagas disease patients, and the physicians who care for them.

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