Although cohort studies suggest that the overall risk is linked to the cumulative total dose, ototoxicity can occur unpredictably at low doses and is often permanent (2). With respect to treatment of infective endocarditis, further evidence is required to support non-aminoglycoside–based regimens, the use of shortened courses, and single daily dosing regimens of gentamicin, all of which may limit toxicity (3–5). In patients with infective endocarditis in whom gentamicin use is unavoidable, we fully concur that informed consent, close monitoring of renal function, and alerting patients to symptoms of ototoxicity (tinnitus, hearing impairment, oscillopsia, or loss of balance) are essential components of care.

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http://dx.doi.org/10.1016/j.jacc.2017.04.057

Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Cahill TJ, Baddour LM, Habib G, et al. Challenges in infective endocarditis. J Am Coll Cardiol 2017;69:325–44.

2. Bertino JJS, Booker LA, Franck PA, Jenkins PL, Franck KR, Nafziger AN. Incidence of and significant risk factors for aminoglycoside-associated nephrotoxicity in patients dosed by using individualized pharmacokinetic monitoring. J Infect Dis 1993;167:173–9.

3. Fernández-Hidalgo N, Almirante B, Gavaldà J, et al. Ampicillin plus ceftriaxone is as effective as ampicillin plus gentamicin for treating enterococcus faecalis infective endocarditis. Clin Infect Dis 2013;56:1261–8.

4. Olaison L, Schadewitz K, Swedish Society of Infectious Diseases Quality Assurance Study Group for Endocarditis. Enterococcal endocarditis in Sweden, 1995–1999: can shorter therapy with aminoglycosides be used? Clin Infect Dis 2002;34:159–66.

5. Dahl A, Rasmussen RV, Bundgaard H, et al. Enterococcus faecalis infective endocarditis: a pilot study on the relationship between duration of gentamicin treatment and outcome. Circulation 2013;127:1810–7.

Pharmacodynamics and Follow-Up Period in the Treatment of Human *Trypanosoma Cruzi* Infections With Posaconazole

The paper by Morillo et al. (1) describes the results of a clinical trial that evaluated the safety and efficacy of posaconazole, benznidazole, and their combination for the etiological treatment of chronic Chagas disease caused by the kinetoplastid parasite *Trypanosoma cruzi*, which is the largest parasitic disease burden in the American continent (2). The study was relevant for the management of this prevalent and long-neglected disease, and was well carried out, but several issues in the experimental design and interpretation of the findings deserve further discussion.

There is a most plausible explanation for the lack of sustained antiparasitic activity of posaconazole in this trial and a previous trial in humans (3), in contrast to the curative activity previously demonstrated in several murine models. Posaconazole was administered at the optimal dose for humans in its liquid suspension formulation (400 mg twice daily); systemic exposures in humans at that dose are 10% to 20% of those measured in mice at the curative anti–*T. cruzi* dose of 20 mg/kg per day [see references in (2)]. This indicates that the patients in both trials were underdosed with posaconazole as anti–*T. cruzi* therapy. The recent development of a delayed-release tablet formulation of the drug, with a 4-fold higher oral bioavailability than the liquid suspension formula, and no toxic side effects up to at least 400 mg/day (4), provides a way to assess the true efficacy of posaconazole for the anti–*T. cruzi* indication.

As the investigators acknowledged, the short follow-up time of 1 year did not permit the evaluation of the effect of the different treatments on the long-term clinical evolution of the patients, but it must be pointed out that it also impeded the assessment of their short-term effects on the patients' parasite burdens. It would have been of critical interest in the current study to assess if the frequent and increasing number of relapses of parasitemia observed among chronic patients treated with benznidazole monotherapy 2 to 5 years after EOT (end of treatment) in the recently completed BENEFIT (Benznidazole Evaluation for Interrupting Trypanosomiasis) trial (5) disappeared or were significantly diminished in patients who received the combination of benznidazole plus posaconazole.

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http://dx.doi.org/10.1016/j.jacc.2017.03.611

Please note: Dr. Urbina has reported that he has no relationships relevant to the contents of this paper to disclose.

JACC VOL. 70, NO. 2, 2017
JULY 11, 2017:293–300

REFERENCES

1. Morillo CA, Waskin H, Sosa-Estani S, et al. Benznidazole and posaconazole in eliminating parasites in asymptomatic *T. cruzi* carriers: the STOP-CHAGAS trial. J Am Coll Cardiol 2017;69:939–47.

2. Urbina JA. Recent clinical trials for the etiological treatment of chronic Chagas disease: advances, challenges and perspectives. J Eukaryotic Microbiol 2015;62:49–55.

3. Molina I, Gómez i Prat J, Salvador F, et al. Randomized trial of posaconazole and benznidazole for chronic Chagas' disease. N Engl J Med 2014;370:1899–908.

4. Guarascio AJ, Slain D. Review of the new delayed-release oral tablet and intravenous dosage forms of posaconazole. Pharmacotherapy 2015;35:208–19.

5. Morillo CA, Marin-Neto JA, Avezum A, et al. Randomized trial of benznidazole for chronic Chagas' cardiomyopathy. N Engl J Med 2015;373:1295–306.