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Fexinidazole: A New Drug for African Sleeping Sickness on the Horizon

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Abstract

Decades after the last new chemical entity was added to the pharmacopeia for human African trypanosomiasis (or sleeping sickness), orally dosed fexinidazole stands poised to replace the current treatment regimen for *Trypanosoma brucei gambiense* infections, following a positive phase 2/3 clinical trial.

Perhaps at one time one of the most neglected of neglected tropical diseases (NTDs) – human African trypanosomiasis (HAT, or sleeping sickness) – has attracted significant attention over the last decade or so from the World Health Organization and public–private partnership organizations such as the Drugs for Neglected Diseases initiative (DNDi). These organizations, working with partners in academia and industry, have brought forward compounds that are in mid-to-late clinical trials. Optimism is high that a solution is indeed near, with the global health community daring to utter the word ‘eradication’ in the same sentence with HAT.

HAT is a parasitic disease that is transmitted by the tsetse fly (*Glossina* spp.), and has a fluctuating prevalence in sub-Saharan Africa; present estimates are now under 4000 cases per year [1]. The disease is caused by two subspecies of *Trypanosoma brucei*: *T. b. gambiense* (which causes the most prevalent, chronic form of the disease), and *T. b. rhodesiense* (a much more virulent and less common subspecies). Both forms of the disease progress through an initial, early stage involving infection of the blood and lymph systems, evolving into a late stage central nervous system (CNS) infection where the characteristic symptoms emerge: sleep disruption, confusion, coma and, if untreated, death. Since most patients are diagnosed during the CNS-involved stage, brain-penetrant drugs are required. This has resulted in a bifurcated pharmacopeia, with the bloodstream infection being treated with the non-brain-penetrant drugs suramin and pentamidine, whereas the CNS infection has been treated using eflornithine (with or without nifurtimox) or melarsoprol (a toxic arsenic-containing agent that has a 5.7% mortality rate) [2]. The latter drug, until the recent implementation of the nifurtimox/eflornithine combination therapy (NECT), was the only

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therapeutic available for *T. b. gambiense* infections. The first new drug regimen for HAT in nearly two decades, NECT represented a significant achievement, for, in addition to essentially replacing melarsoprol, it also reduced the length of the eflornithine dosing regimen by 50%. This was a significant achievement, since a typical course of eflornithine monotherapy was 14 days of intravenously administered eflornithine with a dose of 400 mg/kg per day [3].

In the field of NTDs, repurposing drugs has had a long history of success, including eflornithine itself (originally developed for cancer and now used as a topical agent for hirsutism), as well as the antifungal agent amphotericin B for leishmaniasis, or the veterinary worming agent ivermectin, for river blindness. In the late 1970s, fexinidazole was identified as a broad spectrum anti-infective agent [4], including for HAT [5]. The drug was deemed safe and effective in late preclinical experimentation, yet, due to the lack of commercial viability, it was shelved by the company that discovered it (Hoechst AG, now Sanofi Aventis). Fast-forward nearly 30 years, DNDi evaluated a collection of about 700 nitroaromatic compounds for their potential as antiparasitic agents. Fexinidazole was among these, and was hereby ‘rescued’ as a likely clinical candidate [6].

DNDi researchers and their partner organizations fully characterized fexinidazole in terms of its animal pharmacokinetics and its toxicity and safety profile, with a keen focus on potential genotoxicity (often identified as a liability in nitroaromatic compounds) [6]. Indeed, the compound showed an excellent safety profile, with no such genetic toxicity. In addition, the pharmacokinetic experiments demonstrated that fexinidazole is converted *in vivo* into two active metabolites, both of which display approximately equal *in vitro* potency to fexinidazole itself (though *in vivo* efficacy of these metabolites was lower than the parent drug) [7]. This leads to a lengthy combined exposure time over which antiparasitic activity can be exerted. The compound was progressed into a phase 1 clinical trial, tested in a population of healthy adults of African origin, and well-tolerated doses provided sufficient drug exposure to expect efficacy in humans [8].

Of note to this Spotlight, oral fexinidazole was progressed into a comparative phase 2/3 clinical trial, tested side-by-side with NECT, the best current treatment [9]. The goal was to demonstrate that fexinidazole showed approximately equal efficacy and safety, so that it could replace NECT. Such replacement would eliminate the need for intravenous drug dosing (which requires skilled healthcare personnel and hospitalization to reduce the likelihood of infection), and it would also reduce the overall drug burden that is imposed by eflornithine treatment. In addition, an effective, orally dosed drug would potentially open the door to home-based therapies, and one that could be used for infections without the necessity of definitive stage diagnosis. Taken together, such a drug should improve patient compliance and outcomes.

In the trial though, clinicians and patients knew the drug regimen they were receiving (in an ‘open label’ trial, since the dosing modalities are so obviously different between fexinidazole and NECT). Patient recruitment for this study was non-trivial, given the relatively small pool of HAT patients, and civil unrest in the regions of study. In the end,

over *half a million* patients were prescreened; 395 patients were enrolled on the basis of predefined inclusion criteria.

Participants were randomized to the fexinidazole or NECT arms on a 2:1 ratio, and each received a 10-day regimen of the respective treatment. Patients were observed for 18 days, to ensure parasitological cure, and were tracked for periodic follow-up visits, with an 18-month primary endpoint. For the treatment to be deemed successful, patients must have survived to at least 18 months, with no trypanosomes present in body fluids, and a CSF white blood cell count under 20 cells/ μ l. Additionally, a successfully treated patient must not have required rescue medication. At the outset, the study design allowed for a window of 13% inferiority for fexinidazole based on regional healthcare providers with experience treating HAT. This window was deemed acceptable due to the offsetting convenience of an orally dosed regimen. The clinical trial was deemed successful: fexinidazole treatment led to 91.2% positive outcomes versus 97.6% for NECT. The prevalence of treatment-related adverse events was no different between cohorts, and those that appeared were mild to moderate, and self-resolving.

While fexinidazole enters phase 3b trials to test the feasibility of home-based treatments, a new drug application should be expected shortly. If approved and registered, fexinidazole would represent the only orally dosed monotherapy available for treatment of *T. b. gambiense* HAT, and the first new chemical entity approved for the disease since the early 1980s. The implementation of a drug such as fexinidazole could push HAT to the brink of elimination.

The success with fexinidazole should underscore the power of rescuing compounds that have been shelved for one reason or another. It should be noted that some drugs ‘fail’ clinical trials for a variety of diseases, not because they are toxic or lack oral bioavailability in humans, but rather because they may not reach their targeted clinical endpoints. Such compounds can represent privileged repurposing starting points. Organizations such as DNDi are undoubtedly engaging the drug industry to take a close look at their late-preclinical compound collections to see whether similarly powerful societal benefits could be garnered for other neglected tropical diseases, such as Chagas’ disease, leishmaniasis, lymphatic filariasis, and others.

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