SLEEPING SICKNESS

The last steps towards innovative oral therapies

October 2017
I came to the hospital with my wife and I was diagnosed with sleeping sickness. My wife cried when she heard it. I’m the one who provides food for my nine children – being in the hospital means I can’t provide for them.

Pablo Loela, 50 years old, a subsistence farmer, is receiving treatment for sleeping sickness at Masamuna hospital in Kwilu province in the Democratic Republic of Congo. Pablo started sleeping during the daytime and began getting splitting headaches, vertigo and stomach pains, so he came to the hospital. Pablo had to stay 10 days at hospital to complete his treatment, 10 days away from his work to feed his family.
A DEADLY DISEASE

Sleeping sickness (also known as human African trypanosomiasis or HAT) is caused by two subspecies of parasite, both transmitted by the tsetse fly: *Trypanosoma brucei gambiense* (g-HAT), which accounts for 98% of reported sleeping sickness cases, and *T. b. rhodesiense* (r-HAT).

g-HAT is endemic in 24 countries of West and Central Africa; r-HAT in 13 countries of Eastern and Southern Africa. The majority of patients live in the Democratic Republic of Congo, where 83% of cases are reported, followed by the Central African Republic, Guinea and Chad.

Sleeping sickness affects poor, often marginalized and rural populations, prolonging a vicious circle of disease and poverty.

The disease occurs in two stages. The early, haemo-lymphatic stage (or stage 1) has symptoms such as fever or chills that make it hard to distinguish from malaria or other diseases, and as a result is often missed or misdiagnosed.

In the later meningo-encephalitic stage (stage 2), the parasite crosses the blood-brain barrier and causes serious neurological disorders including sleep cycle disruptions, neurological manifestations, and progressive mental deterioration.

Sleeping sickness is usually fatal if left untreated.
A BRIEF HISTORY OF SLEEPING SICKNESS

The history of sleeping sickness is one marked by the appearance of deadly epidemics interspersed by decades where the disease seems largely under control.

Colonial era
In the 1890s, 500,000 people in what is then the Belgian Congo and more than 200,000 in British-controlled Uganda die from sleeping sickness. In the 1920s, mobile teams are established and follow the “Jamot Method” of systematic active case detection and treatment, with the ultimate objective the elimination of the parasite from the human reservoir.

1990s
The withdrawal of external aid leads to a collapse of the mobile team system, with conflict and instability fueling further resurgence of sleeping sickness. A new epidemic occurs with a spike of 35,000 reported cases a year, including some villages reporting case levels as high as 50% of the entire population.

1960s
This approach succeeds in reducing the number of cases to below 5,000 per year. This decrease in prevalence, along with severely constrained resources following the independence of most endemic countries, means activities including vector control and mobile teams are drastically reduced, causing generalised resurgence of the disease.

2000s
The World Health Organization (WHO) signs donation agreements with pharmaceutical companies such as Aventis (later Sanofi) and Bayer to access treatments and control the disease. Donors, in particular Belgium, renew their support. In 2009, a new combination therapy known as NECT, developed by DNDi and partners, is introduced, replacing an arsenic-based highly toxic treatment that killed one in every 20 patients. The number of reported cases drops below 10,000 for the first time in decades.

2010s
In 2012, WHO launches its Roadmap, a comprehensive plan of control, elimination and eradication targets for 17 NTDs - including sleeping sickness - to be reached by 2020. Leaders from global health and development organizations and the pharmaceutical industry pledge in the London Declaration to work to reach WHO’s 2020 elimination goals for 10 NTDs. By 2016, fewer than 2,500 new cases of HAT (g-HAT) are reported.
Before 2009, the best treatment for sleeping sickness, eflornithine, was extremely complex to distribute and administer in regions affected by the disease. All-too-often, doctors would have no choice but to use melarsoprol, a highly toxic, arsenic-based drug. Treatments improved radically in 2009, when Epicentre/MSF/DNDi clinical trials demonstrated the safety and efficacy of a simpler and shorter nifurtimox and eflornithine combination therapy (NECT).

DNDi’s longer-term R&D strategy remains to identify and develop two entirely new oral drugs that are effective against both stages of the disease, both parasite subspecies, and can be used at home. Today, with fexinidazole and acoziborole, that ambitious objective is almost within reach.

**Before 2009: toxic or complex treatments**

**Melarsoprol** – so painful that it was dubbed “fire in the veins”, this arsenic derivative killed 1 in 20 patients.

**Eflornithine** – difficult to transport, distribute and administer, as it required 14 days of hospitalization and 56 intravenous infusions.

**The first treatment revolution: NECT**

Now used to treat 100% of all stage-2 patients with g-HAT in all endemic countries.

Safe, effective, and simpler for patients and for health staff.

But treatment remains cumbersome, difficult to ship, store and administer; patients must still be hospitalized to receive the intravenous infusions, as well as undergo a lumbar puncture first to determine the stage of the disease.

The need to bring a simple, safe, and effective treatment as close as possible to the patient’s bedside remains.

**New game-changing oral therapies**

New safe and effective oral therapies that work for both diseases stages will bring treatment out of the hospital, closer to patient’s bedside.

**Fexinidazole – the first all-oral cure**

The result of DNDi’s compound mining activities, fexinidazole will – once it is approved – remove the need for hospitalization, potentially even enabling some patients to take their treatment at home. Therapy will consist of one daily dose of pills for ten days, and will be the same for both stages of the disease, meaning no more lumbar punctures.

**Acoziborole – one dose for a cure?**

Acoziborole is the first DNDi new chemical entity resulting from its own lead optimization programme to enter clinical development. Thanks to an unusually long half-life when tested in healthy volunteers, acoziborole could be administered as a single dose. If proved safe and effective, acoziborole will become a key tool to sustain the elimination after 2020.
FEXINIDAZOLE: 
THE FIRST ALL-ORAL TREATMENT 
FOR SLEEPING SICKNESS

If it is successfully approved, fexinidazole will become the first new chemical entity to have been developed by DNDi, which has steered its progression through all stages of the drug development pipeline from lab to patient. The ‘fexi’ story is one which illustrates the benefits of DNDi’s alternative R&D approach that puts patient needs at the centre and harnesses the capacities of actors from all sectors, including pharmaceutical companies, medical humanitarian organizations, Ministries of Health of endemic countries, and the World Health Organization.

2005
DNDi begins ‘compound mining’ to profile activity against the sleeping sickness parasite in more than 700 different potential compounds from 15 different sources in academia and industry, in collaboration with the Swiss Tropical and Public Health Institute (Swiss TPH). These efforts lead to the identification of fexinidazole, on which Hoechst (now Sanofi) had initiated pre-clinical development in the 1970s, but which had not entered clinical studies.

2009
DNDi and Sanofi team up on development and manufacturing.
A collaboration agreement for the development, manufacturing and distribution of fexinidazole gives DNDi the responsibility for pre-clinical, clinical, and pharmaceutical development, while Sanofi handles industrial development, registration, and production of the drug.

2007
Pre-clinical studies begin.
Sanofi provides initial samples, data, and advice based on the previous Hoechst development programme. DNDi performs extensive regulatory toxicology studies, including safety pharmacology and animal studies, showing fexinidazole has a good safety profile.

2010
Phase I studies begin.
DNDi carries out clinical trials assessing the safety and pharmacokinetics of fexinidazole in human volunteers given in single and multiple doses.
2011

DNDi and Sanofi request joint scientific advice from the US Food and Drug Administration and the European Medicines Agency, with WHO support, on the clinical development plan for fexinidazole. This leads to the development of a protocol for a single pivotal Phase II/III study to prove the safety and efficacy of fexinidazole, with NECT as the active comparator.

2012

Phase II/III pivotal clinical study in stage-2 g-HAT begins in the Democratic Republic of Congo (DRC) and Central African Republic (CAR), with the DRC national control programme (PNLTHA) playing a key role in study implementation. 394 patients were recruited at ten clinical sites in the DRC and CAR, with Médecins Sans Frontières supporting the management of two trial sites in hard-to-reach locations.

2014

Complementary cohorts are added to the study.

Two additional cohorts, one in 230 adult patients with stage 1 and early stage 2 of the disease, and another in 125 children between six and 14 years of age, are initiated, in eight of the DRC sites.

2016

A Phase IIIb study on special population groups excluded from previous studies is initiated, including pregnant or lactating women, and patients with poor nutritional status or with chronic diseases. Patients are treated either in hospital, or at home, thereby providing also preliminary information about treatment compliance and final effectiveness in ambulatory patients.

2017

Results confirm that fexinidazole is safe and effective, and presents significant advantages over NECT as it removes both the need for a systematic lumbar puncture and for hospitalization of a patient. The submission of a regulatory dossier to the European Medicines Agency under Article 58 for the treatment of g-HAT (both stages) is prepared.
THE CHALLENGE OF CONDUCTING CLINICAL TRIALS IN REMOTE AND CONFLICT AREAS

The journey to the sleeping sickness trial site in Isangi from the DNDi office in Kinshasa begins in the domestic airport of DRC’s capital city and ends more than a day later halfway across the country in a barge crossing the Congo river. In between: hours spent navigating potholed dirt roads, collapsed bridges, checkpoints, and multiple river crossings. Once at Isangi, canoes must be used to reach many of the patients as there are no roads.

Yet for DNDi’s clinical team in DRC, Isangi is one of the easier-to-reach sites. The DRC and the Central African Republic (CAR) both pose daunting challenges that must be overcome to develop better treatments for patients suffering from sleeping sickness.

Political instability is a major challenge. Armed conflict in CAR forced DNDi to stop recruitment of patients in 2013. “Despite this constraint, we managed to follow-up more than half of the patients who had been treated,” says Dr Francis Regongbenga, Principal Investigator for CAR at the Batangafo site.

A second important challenge is infrastructure. It is imperative that wards, labs, and other facilities conduct clinical research that is up to par with “Good Clinical Practice” (GCP). Clinical trial sites were brought up to these standards – not a small task considering their remote location. Nine referral treatment units were renovated and refurbished, with solar energy equipment and generators installed. Equipment was brought in: defibrillators and tools such as the Piccolo analyser – a fully automated system for blood testing. Internet access was installed to enable transmission of case report forms, particularly necessary for the monitoring of safety parameters.
“With the fexinidazole clinical trial, everything changed. Not only does our hospital no longer look like a farm, but the community benefits from a modern facility and our work is easier,” says Watson Tawaba, nurse at the Bagata site in DRC.

Overcoming the lack of trained staff is another hurdle. Through the HAT Platform – a clinical research network to strengthen capacities in endemic regions set up with the support of DNDi in 2005 – trainings were provided in diagnostic and treatment procedures, pharmacovigilance, GCP guidelines, and even medical waste management.

The joint experience of DNDi and the national sleeping sickness programme in the DRC shows it is possible to build an environment conducive to running quality clinical trials. These efforts build and sustain the capacity to conduct a high standard of clinical research in endemic countries, but they also bring lasting benefits to researchers, staff and hospitals, as well as to health systems more broadly, and thus ultimately to local communities and patients.
LOOKING TO THE FUTURE:
ACOZIBOROLE, A SINGLE-DOSE ORAL TREATMENT TO ACHIEVE SUSTAINED ELIMINATION OF SLEEPING SICKNESS

DNDi’s investment into sleeping sickness R&D does not end with fexinidazole.

An oxaborole originally owned by Anacor Pharmaceuticals (later acquired by Pfizer) was found to be active against HAT parasites at the University of California San Francisco, and further investigated by a consortium consisting of DNDi, Anacor, SCYNEXIS, Pace University, and Swiss TPH. Compound optimization involving the examination of over 1,000 compounds produced acoziborole, which was selected as a promising pre-clinical candidate for T.b gambiense sleeping sickness in late 2009.

In pre-clinical studies, acoziborole was shown to be safe and efficacious in treating a brain form of the disease in animals, when administered orally in a single dose. Acoziborole was found to have an unusually long half-life when tested in healthy volunteers.

In March 2012, acoziborole became DNDi’s first new chemical entity resulting from its own lead optimization programme to enter clinical development. Phase I trials on this new chemical entity were completed in 2015, and allowed the therapeutic dose to be determined, administered as a single dose of three tablets. A pivotal Phase II/III trial started in the last quarter of 2016. Seven study sites were initiated in Democratic Republic of Congo. 61 patients (out of a target 350) had been recruited by October 2017.

The submission of a regulatory dossier to the European Medicines Agency under Article 58 is planned for 2021, for the treatment of T.b gambiense HAT (both stages) with acoziborole. Combined with a rapid diagnostic test, acoziborole promises to be a game-changer offering a “foci-based” treatment approach for remote areas, conflict zones and sentinel sites where re-emergence of sporadic cases occur after wider use of fexinidazole.

Acoziborole, if proved safe and effective, will thus be a key tool to achieve a sustained elimination of the disease.
NECT was the first revolution in the treatment of sleeping sickness. Fexinidazole could be the next. The lumbar puncture that all patients fear will no longer be necessary. Treatment will no longer have to take place in the hospital. People will not have abandon their livelihoods to seek treatment. Health staff will be freed up for other tasks. I am full of hope for patients and the national programmes.

Dr Wilfried Mutombo, DNDi Project Coordinator for HAT
A WORD OF THANKS

The development of fexinidazole over the past decade bears witness to the value in forging strong partnerships involving the WHO, endemic country Ministries of Health and national programmes, and the pharmaceutical industry. This accomplishment is far from DNDi’s alone, but is one shared with all our partners and donors.

DNDi wishes to acknowledge the contribution of its R&D partners on sleeping sickness:

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