Institution: London School of Hygiene & Tropical Medicine (LSHTM)

Unit of Assessment: UoA1 – Clinical Medicine

Title of case study: Miltefosine for the treatment of leishmaniasis

1. Summary of the impact

Miltefosine is the first oral drug to be developed for the treatment of leishmaniasis, a worldwide parasitic infection with up to 12m cases. Also developed as a cancer drug, miltefosine was identified and tested for leishmaniasis therapy at LSHTM and has been added to WHO's essential medicines list as a result of subsequent clinical trials. It has been widely used for the treatment of visceral leishmaniasis (VL) in India, Nepal and Bangladesh, and for the cutaneous form of the disease in Latin America. Phase III and IV clinical trials of combination therapies including miltefosine have been carried out in India.

2. Underpinning research

Leishmaniasis is a disease complex caused by 17 different species of protozoan parasites belonging to the genus *Leishmania*, which are transmitted between mammalian hosts by sandflies. An estimated 12m humans are infected, with an incidence of 0.5m cases of the visceral form of the disease (which is fatal if untreated) and 1.5 to 2.0m of the cutaneous form. Leishmaniasis occurs mostly in tropical and subtropical countries.

Research into oral treatment for the disease with miltefosine (a phospholipid drug) was carried out at LSHTM by Simon Croft, Professor of Parasitology (at LSHTM from 1982–1984 and since 1987). The research took part in four phases, the earliest of which began prior to the research assessment period, but is outlined here briefly to provide context.

Discovery

Following the discovery of the anti-leishmanial activity of miltefosine (hexadecyl phosphocholine) by a team led by Croft at the Wellcome Research Laboratories between 1984–1986 (which identified the compound as having selective in vitro and in vivo activity against the causal parasite of VL, *Leishmania donovani*) Croft continued the work at LSHTM. In vitro and in vivo studies funded by WHO Tropical Disease Research Programme (TDR), a programme for research and training in tropical diseases, extended the observations on miltefosine to other similar phospholipid drugs, including ilmofosine, and included recent clinical isolates of *L. donovani* and other trypanosomatid parasites.[3.1, 3.2] Later, Croft and the team also showed that miltefosine was active against the *Leishmania* species that cause cutaneous leishmaniasis, showing differences in susceptibility between species (2002).[3.3]

Development

Independently, pharmaceutical companies were developing miltefosine and other phospholipid derivatives as anti-cancer agents between 1987 and 1996. In 1993–1994 Croft worked with the WHO TDR programme to explore the possibility of clinical development of these anti-cancer drugs with four pharmaceutical companies for VL treatment. As a result, Asta Medica (manufacturers of miltefosine) was invited to participate in a clinical development programme.

Mechanisms of action and resistance

Croft initiated and coordinated two programmes, funded by the EU with partners from South America and Europe, to study the mechanism of action and resistance of *Leishmania* to miltefosine. One partner in the programme, the Institute of Parasitology and Biomedicine in Granada/Spain, importantly identified a membrane transporter (LdMT) responsible for conferring drug resistance to the *Leishmania* parasite, which was shown to be present in the intracellular stage of the parasite in rodent models of infection by the LSHTM team.[3.4, 3.5]

Miltefosine combination therapy

The selection of resistant forms made studies on the potential of drug combinations of anti-leishmanial drugs an important next step. Experimental studies in vitro and in mice with miltefosine

combined with other standard antileishmanials (pentavalent antimonial, paromomycin and amphotericin B), identified combinations that showed significant additive activities against *L. donovani* (e.g. miltefosine and amphotericin B).[3.6] In 2004, Croft was seconded to the Drugs for Neglected Diseases initiative (DNDi) in Geneva for three years (retaining his LSHTM staff position) as the first R&D director of this product development partnership, where he led the project for clinical development of combination therapy.

3. References to the research

3.1 Croft, SL, Snowdon, D and Yardley, V (1996) The activities of four anticancer alkyllysophospholipids against *Leishmania donovani, Trypanosoma cruzi* and *Trypanosoma brucei*, *Journal of Antimicrobial Chemotherapy*, 38(6): 1041–1047, doi: 10.1093/jac/38.6.1041. Citation count: 119

3.2 Escobar, P, Yardley, V and Croft, SL (2001) Activities of hexadecylphosphocholine (miltefosine), AmBisome, and sodium stibogluconate (Pentostam) against *Leishmania donovani* in immunodeficient *scid* mice, *Antimicrobial Agents and Chemotherapy*, 45(6): 1872–1875, doi: 10.1128/AAC.45.6.1872-1875.2001. Citation count: 61

3.3 Escobar, P, Matu, S, Marques, C and Croft, SL (2002) Sensitivities of *Leishmania* species to hexadecylphosphocholine (miltefosine), ET-18-OCH_3 (edelfosine) and amphotericin B, *Acta Tropica*, 81(2): 151–157, doi: 10.1016/S0001-706X(01)00197-8. Citation count: 102

3.4 Seifert, K, Matu, S, Pérez-Victoria, FJ, Castanys, S, Gamarro, F and Croft, SL (2003) Characterisation of *Leishmania donovani* promastigotes resistant to hexadecylphosphocholine (miltefosine), *International Journal of Antimicrobial Agents*, 22(4): 380–387, doi: 10.1016/S0924-8579(03)00125-0. Citation count: 82

3.5 Seifert, K, Pérez-Victoria, FJ, Stettler, M, Sánchez-Cañete, MP, Castanys, S, Gamarro, F and Croft, SL (2007) Inactivation of the miltefosine transporter, LdMT, causes miltefosine resistance that is conferred to the amastigote stage of *Leishmania donovani* and persists in vivo, *International Journal of Antimicrobial Agents*, 30(3): 229–235, doi: 10.1016/j.ijantimicag.2007.05.007. Citation count: 34

3.6 Seifert, K and Croft, SL (2006) In vitro and in vivo interactions between miltefosine and other antileishmanial drugs, *Antimicrobial Agents and Chemotherapy*, 50(1): 73-79, doi: 10.1128/AAC.50.1.73-79. Citation count: 63

Key grants

Croft, An Integrated Screen for the Identification and Evaluation of Novel Antileishmanial and Antitrypanosomal Compounds, WHO/TDR (I-CHEM), 1992–1996, $420,000.
Croft, Antileishmanial and Antitrypanosomal Activities of Alkyllysophospholipids, EU FP4, 1996–1998, €200,000.
Croft, Miltefosine for Leishmaniasis: Molecular Basis of Mechanisms of Action, Resistance and Combination Therapy, EU FP6, 2001–2004, €304,000.
Croft and Yardley, Funding for Pre-clinical Studies and the Leish Drug Combo Working Groups, Drugs for Neglected Diseases initiative (DNDi), five grants, 2004–2013, £602,422.

4. Details of the impact

The research described in Section 2 has directly impacted on WHO drug policies and enabled miltefosine treatment for tens of thousands of people with leishmaniasis in high-incidence countries such as India, Bangladesh and Colombia. It has also had commercial impacts for miltefosine manufacturers, and led to phase III and IV clinical trials in India.

Following clinical trials in the 1990s and 2000s and the registration of miltefosine in India in 2002 (the first new drug for visceral leishmaniasis in 40 years), the governments of India, Nepal and Bangladesh agreed a 10-year programme to eliminate leishmaniasis by 2015. Miltefosine was adopted as the only drug to be included in this VL elimination programme – a decision in which the

research by Croft and colleagues played a significant part.[5.1, 5.2] The drug has since been used to treat about 25,000 patients per year through government-run centres – a total of more than 137,000 between 2008 and mid-2013. Miltefosine is also available on the private market, although it is not known how many patients benefit through this route.

In 2010, an application was made by the manufacturers of miltefosine, Paladin Laboratories in Montreal, Canada, to include the drug on the WHO's Model List of Essential Medicines, a directory of drugs which – according to WHO – should be available within the context of functioning health systems at all times in adequate amounts. The WHO Expert Committee charged with the selection of essential medicines reviewed the evidence (including the Croft research outputs) and approved miltefosine, which has since been included in two editions of the list in March 2011 and April 2013.[5.3] The list is essential for the funding and distribution of the drug by international organisations such as Médecins Sans Frontièrs (MSF) who follow the WHO list. The list is also used by Ministries of Health in individual countries to assemble their own essential drugs lists.

Also in 2010, Croft was invited to serve on another WHO Expert Committee, which produced a technical report on *Control of the Leishmaniases*.[5.4] This is a key public health advisory document used by governments in countries affected by leishmaniasis, with miltefosine treatment playing an important part in it – again on the basis of Croft's research.

These endorsements led to considerable commercial benefits for the manufacturers of miltefosine, Paladin Laboratories. (Asta Medica, originally selected by WHO for the development process, had sold their rights to Zentaris in 2001, and Zentaris was subsequently acquired by Paladin.) According to its own records, the company sold about 100,000 treatments directly to governments between 2008 and the middle of 2013, with the most recent sales level at 17,000 per annum.[5.5] This excludes private sector sales, which are difficult to measure.

Phase III and IV clinical trials on anti-leishmanial drug combinations which include miltefosine, aimed at reducing the length of course of treatment and prevention of drug resistance, were carried out in India beginning in 2009–2010. The phase III trials showed AmBisome + miltefosine and paromomycin + miltefosine combinations giving a >98% cure rate.[5.6] These combinations are part of a phase IV clinical trial beginning in July 2013 and could reduce the courses of treatment from 28 days to 8 days.

Miltefosine is also used for the treatment of cutaneous leishmaniasis (CL), especially in South America.[5.7] In Colombia, it has become the drug of choice for this disease as a result of Croft and colleagues' research, and has been shown to achieve a cure rate of 84–91% *for L. panamensis*. Argentina's Ministry of Health recommended miltefosine as the drug of choice for CL in a 2010 guide for health professionals.[5.8] The drug has also undergone extensive clinical trials in other countries, in particular Brazil and Bolivia[5.9] against CL and mucocutaneous leishmaniasis (MCL) caused by *L. braziliensis* and *L. guyanensis*.

In East Africa, miltefosine has been used in clinical trials to improve treatment of HIV VL co-infected patients, proving to be as effective as, and less toxic than, the standard antimonial drugs.

Croft has worked to raise awareness and understanding of leishmaniasis treatment among medical practitioners and the general public in a variety of ways, including through presentations at 12 international practitioner meetings and symposia during the impact assessment period, and media interviews (BBC online August 2009), as well as a YouTube video recorded for an exhibition on neglected tropical diseases at the Royal Festival Hall in London in July 2010.[5.10]

5. Sources to corroborate the impact (indicative maximum of 10 references)

5.1 Former Director, National Institute for Medical Research, India; was Director at time of clinical trials and can corroborate importance of miltefosine and role of Croft.

5.2 Staff member, WHO TDR can also corroborate role of LSHTM findings in Indian decision to use miltefosine in elimination programme.

5.3 WHO (2013) *WHO Model List of Essential Medicines: 18th list (April 2013)*. Geneva: WHO, http://www.who.int/medicines/publications/essentialmedicines/18th_EML_Final_web_8Jul13.pdf (accessed 29 October 2013).

5.4 WHO (2010) *Control of the Leishmaniases: Report of a Meeting of the WHO Expert Committee on the Control of Leishmaniases, Geneva, 22–26 March 2010,* WHO Technical Report no. 949. Geneva: WHO, http://whqlibdoc.who.int/trs/WHO_TRS_949_eng.pdf (accessed 29 October 2013) (p. 56ff. Croft acknowledged as member Expert Committee p. vii).

5.5 Statement from Paladin Laboratories can be made available to the panel on request.

5.6 Sundar, S, Sinha, PK, Rai, M, Verma, DK, Nawin, K, Alam, S, Chakravarty, J, Vaillant, M, Verma, N, Pandey, K, Kumari, P, Lal, CS, Arora, R, Sharma, B, Ellis, S, Strub-Wourgaft, N, Balasegaram, M, Olliaro, P, Das, P and Modabber, F (2011) Comparison of short-course multidrug treatment with standard therapy for visceral leishmaniasis in India: an open-label, non-inferiority, randomised controlled trial, *Lancet*, 77(9764): 477–486, doi: 10.1016/S0140-6736(10)62050-8.

5.7 Head of Leishmaniasis Clinical Program, DNDi (Drugs for Neglected Diseases initiative).

5.8 Dirección de Epidemiología (2010) *Enfermedades infecciosas leishmaniasis visceral: Diagnóstico de Leishmaniasis Visceral,* Guia para el equipo de salud, no. 5 (Spanish), Ministerio de Salud de la Nación, Argentina, http://www.msal.gov.ar/images/stories/epidemiologia/pdf/guia-leish.pdf (accessed 29 October 2013) (p. 16).

5.9 Machado, PR, Ampuero, J, Guimarães, LH, Villasboas, L, Rocha, AT, Schriefer, A, Sousa, RS, Talhari, A, Penna, G and Carvalho, EM (2010) Miltefosine in the treatment of cutaneous leishmaniasis caused by *Leishmania braziliensis* in Brazil: a randomized and controlled trial', *PLoS Neglected Tropical Diseases*, 4(12): e912, doi:10.1371/journal.pntd.0000912.

5.10 Imperial College London (2010) Leishmania: lessons from a parasite – videos and Interviews, http://wwwf.imperial.ac.uk/theoreticalimmunology/exhibit2010/?page=video (accessed 29 October 2013).