Progress in Neglected Diseases Research and Development: Towards the Elimination of Kinetoplastid and Filarial Diseases

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Summary

The WHO roadmap has set ambitious goals to eliminate a number of neglected diseases (NDs), which will require improved treatments and increased implementation at the primary healthcare level to access remaining patients as numbers decrease.

A “fatal imbalance” between drugs needed by the poor and R&D efforts was previously described, with only 1.1% of drugs approved over 1975-1999 for NDs, despite accounting for 12% of the global health burden. A review of the next decade’s progress shows that the advent of new models, such as Product Development Partnerships (PDPs), and philanthropic efforts has led to an improvement, but our study shows that still only 4% of the 850 products registered (2000-2011) were indicated for NDs, mostly repurposed products.

‘The Fatal Imbalance’

Trouiller et al (2002): only 1.1% of all drugs approved over 1975-1999 were for “neglected diseases” accounting for 12% of the global health burden.

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Objective

To reassess the state of R&D for neglected diseases compared to other diseases over 2000-2011 based on (A) Approved products and (B) Ongoing clinical trials.

Methods

Selection of diseases

49 infectious and parasitic diseases, selected out of existing lists:

5 disease categories

Approved products

• All products approved across all indications from 1 Jan 2000 to 31 Dec 2011

Clinical trials review

Data bases: (Sep 1999-Dec 2011)

• Phase I-II clinical trials listed in the US National Institutes of Health (NIH) (ClinicalTrials.gov)

• WHO registry of clinical trials

• 31 December 2011 “Snapshot” of active trials

Clinical trial sponsors were classified according to organization type

Results

(A) Approved products

Deficit persists

NDS represented 11% of the global burden of disease in 2004. But of the 850 new therapeutic products registered in 2000-2011, 37 (4%) were indicated for neglected diseases, comprising 25 products with a new indication or formulation and eight vaccines or biological products.

Only four new chemical entities were approved for neglected diseases (three for malaria, one for diarrheal disease), accounting for 1% of the 336 new chemical entities approved during the study period.

Excluding vaccines

48% of new products for ND in WHO-EMR vs 4% for all other diseases

(B) Clinical trials

Of 548 445 clinical trials registered in Dec 31, 2011, only 2016 (1%) were for neglected diseases

Targets and milestones for elimination and eradication of NTDs 2015-2020

WHO 2020 targets include the global elimination of human African trypanosomiasis (HAT) and lymphatic filariasis (LF), and regional elimination of visceral leishmaniasis (VL) (India) and onchoceriasis in selected African countries and Yemen by 2020 and Latin America by 2030.

Conclusions

• A persistent imbalance between disease burden and product development for neglected diseases.

• Positive advances are primarily based on repurposed products.

• A major R&D gap remains in NCEs for neglected diseases.

• Malaria, TB, and diarrheal diseases remain the primary focus of product-development research, with little and in some cases no focus at all on other neglected diseases.

NCE’s for HAT

• Fexinidazole, identified from compound mining efforts, entered a pivotal Phase II/III study in 2012 and is currently recruiting patients with advanced T. gondii HAT in the DRC and the CAR. Two complementary studies will examine efficacy and safety in adults with stage 1 and early stage 2 HAT, and children aged 6-14 years.

• SCYX-7158 successfully progressed through pre-clinical development, entering Phase I clinical development in early 2012, which is nearing completion.

NCE’s for Leishmaniasis

Visceral leishmaniasis (VL)

• Fexinidazole in Proof of Concept for VL in East Asia

• VL 2008: First class of compounds to show sterile cure in animal models of VL. Scheduled for first-in-man in 2015

Cutaneous leishmaniasis (CL)

• Anfotericin B liposomal formulation containing Amphotericin B in Phase I testing in Columbia

• CPG-055: Immune-modulatory therapy based on a 35 base oligonucleotide that stimulates the innate immune system via toll-receptor activation in pre-clinical testing

New treatments for Chagas Disease

• Fexinidazole Monotherapy (NCE) – Phase II Proof of Concept trial in Bolivia – to test efficacy and safety of 6 dosing regimens

• Benznidazole - New Regimens

• Proof of Concept – Phase IV

• Improve safety, tolerability and compliance

• Maintain efficacy compared to current regimen

• Select the optimum combination of dose, dosing frequency and treatment duration

• Combination Therapy of Aslool E1224 (NCE) and BZN

– Proof of Concept – Phase II

– Reduction of dose and duration of therapeutic regimen

– Improvement of safety and tolerability

• Potential reduction of resistance development for the individual components of the combination

NCE for Filariasis

• Emodepside is a natural product in veterinary use and is under pre-clinical evaluation and due to enter the clinic in 2015