A Review of 21 Years of TDR/WHO and ICMR Sponsored Filariasis Research at T. D. Medical College, Alappuzha

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ABSTRACT

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'Filariasis Chemotherapy Unit' (FCU), the lymphatic filariasis (LF) research unit, sponsored by the TDR/WHO and ICMR was established in T. D. Medical College Hospital, Alappuzha in 1989. This centre is now well recognized both at national and international levels being the only one in the world conducting clinical research in Brugian filariasis. Till date, 19 research projects have been completed in this unit successfully, in the span of last 21 years and presently there are two ongoing projects. This unit is recognized by TDR/WHO and NICD for training in LF disability management, because of the pioneering work done here.

Keywords: Filariasis, Trials, Treatment protocols, Disability management

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INTRODUCTION

'Filariasis Chemotherapy Unit' (FCU), the lymphatic filariasis (LF) research unit, sponsored by the TDR/WHO and ICMR was established in T. D. Medical College Hospital, Alappuzha in 1989. This was following the recommendations of the 12th Scientific Advisory Committee (SAC) Meeting held at the Vector Control Research Centre (VCRC), Pondicherry on 29-4-1988, in which the then Secretary of Health, Govt. of Kerala was a special invitee. On behalf of the Government of Kerala, the Secretary of Health had agreed to provide all support to start a project at T.D.Medical College, Alappuzha to undertake research work in the prevention and treatment of Brugian filariasis. A public health problem of national priority, filariasis is endemic in the coastal belt of Alappuzha district, the Ambalapuzha and Cherthala Taluks of which are well-known pockets of *Brugiamalayi* (BM) infection. As the Head of Department of Medicine, I was designated as the Principal Investigator of this project when it was started in August 1989, consequent on the order from the Director of Medical Education (DME). I am continuing this voluntary work till date, as the Principal Investigator of the project even after my retirement from Govt. service in 1994. This is based on the recommendation from TDR/WHO and permission granted by the Kerala Government, time to time. Dr. T.K.Suma, Associate Professor of Medicine has been associated with this research work as Co-investigator.

This centre is now well recognized both at national and international levels being the only one in the world conducting clinical research in Brugian filariasis. Till date, 19 research projects have been completed in this unit successfully, in the span of last 21 years and presently there are two ongoing projects. The results of all these studies are already published in international medical journals of repute. The outcome of these studies has been presented during various national and international conferences. Scientists from ICMR and various countries including TDR/WHO, NIH/USA, UK, Japan, Poland, African States and Brazil have visited this centre for discussions, exchange of ideas and collaborative research in filariasis.

This research centre had collaborated with ICMR institutions like Tuberculosis Research Centre, Chennai; VCRC, Pondicherry; Regional Medical Research Centre (RMRC), Bhubaneswar; and also PGI Chandigarh and National Institute of Communicable Diseases (NICD), New Delhi. Some studies were undertaken in collaboration with London School of Hygiene & Tropical Medicine; University of IOWA, USA and University Sains Malaysia. This unit had organized two TDR sponsored international workshops at Alappuzha, first one for LF disability protocol development and the second for training in LF disability management.

Apart from research activities, this unit has been conducting regular outpatient sessions, twice a week to examine and treat patients suffering from filariasis.

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Night blood examination to detect microfilaria (mf) is done twice every week regularly and also by conducting camps at night in rural areas. During the last 21 years a total of 16,007 patients with Filariasis are examined and treated. So far 690 microfilaria detection camps are held at night, in which blood smears of 41,609 people are examined and a total of ~600 mf positive persons are identified and treated, which included 113 children. This unit is recognized by TDR/WHO and NICD for training in LF disability management, because of the pioneering work done here.

Summary of the research work undertaken in this unit

As mentioned above, so far 19 research projects have been completed in this unit and there are two ongoing projects. The studies carried out included different aspects of LF as summarized in table 1 below. All studies were conducted after submitting the concerned protocols and informed consent forms to both the TDMC Institutional Ethics Committee as well as TDR/WHO Ethics Review Committee and after obtaining their approval. Copies of the annual reports submitted to TDR/WHO were regularly forwarded to DME through the Principal, T.D. Medical College.

Table 1. Different aspects of LF research carried out in this research unit

Sl. No.	Titles of the groups	No. of studies
1	Different drug trials for treatment of micro-filaraemia	8
2	Studies for disability management in filarial disease	4
3	Socio-economic aspects of filarial disability	1
4	Ultrasound examination for adult worms	1
5	Pharmacokinetic study of antifilarial drugs	1
6	Immunological studies	2
7	Diagnostics for Brugiamalayiinfection	1
8	Wolbachia related study	1
9	Study on lymphatic filariasis in children	1
10	ICMR Monograph on Indian medicinal plants used in treatment of lymphatic filariasis	1
	Total number of projects	21

List of references for research papers published from the completed studies is provided at the end of the article and the reference numbers are indicated in the text. Further details of the studies can be accessed through these references.

1. Drug trials for treatment of microfilaraemia: The eight studies consisted of administration of the antifilarial drugs diethylcarbamazine (DEC), ivermectin and albendazole (ABZ) either as single drugs or in different combinations to subjects with BM microfilaraemia. This was to assess their efficacy in different dose ranges and frequencies of administration and to observe adverse reactions if any, in hospital based trials with proper laboratory back up.

i. Study to determine the optimum dose of ivermectin effective in clearing the mf of BM infection (1989-90). This was consequent on successful single dose ivermectin studies in *Wuchereria bancrofti* (WB) microfilaraemia conducted at Chennai[1]

ii. Retreatment with single dose of ivermectin at 6th month and follow up for one year (1990-91).

iii. These two studies indicated that single dose ivermectin 200µg/ kg resulted in mf clearance of 50% at 6 months and 65% at end of another 6 months after retreatment, indicating the efficacy of single doses of ivermectin. Adverse reactions were minimal.[1]

iv. Comparative study of single doses of ivermectin 400 µg /kg versus single dose of DEC 6 mg /kg and follow up for one year (1991-92). Both drugs resulted in prolonged suppression of mf even at the end of one year (mf clearance for ivermectin 95.4% and DEC 97.05%). Adverse reactions were mild to moderate. It was concluded that single doses of DEC were as good as ivermectin and equally safe.[2]

v. Study to assess efficacy, tolerability and safety of DEC medicated salt in treatment of BM microfilaraemia (1995-96). This study was initially hospital based and then followed up for one year. Conclusion was that at the end of one-year, substitution of DEC salt in food (instead of common salt) resulted in 80% clearance of mf. The mild adverse reactions in individuals depended on the severity of parasitaemia.[3]

vi. Study of combination of single doses of DEC (6 mg/kg) and ivermectin (400 µg/kg) and one year follow up (1995-97). Mf clearance by this combination in single dose was superior to that of either drug alone (99.9%). Adverse reactions noted were due to rapid mf clearance. Conclusion was that combining the two drugs was more efficacious than either drug alone.[4]

vii. Comparative study of efficacy of single doses of combinations of a) ivermectin with DEC, b) ivermectin with ABZ or c) DEC with ABZ and follow up for one year (1996-98). It was found that

the two DEC groups caused better mf suppression at the end of one year. Adverse reactions were mild to moderate and were more in the two DEC groups with better mf clearance.[5]

viii. Retreatment of the subjects in the above study (vi) with a second dose of same drugs they received during the first year and follow up for another year. This was to assess the efficacy of retreatment with antifilarial drugs (1998-99). Conclusion from this study again was that the two DEC containing groups caused best mf suppression at the end of 2nd year. Interestingly there were fewer adverse reactions after the second dose since mf load left to be cleared was much less than during the first year of treatment.[6]

ix. Effect of albendazole dose and interval on Brugia malayi microfilarial clearance in India: a randomized, open label study with a two-year follow up period. This is one of the ongoing studies in this unit presently, which was initiated on 04-04-2008. This is meant to find out the most effective dose and frequency of ABZ in combination with DEC 6 mg/ kg for administration under mass drug therapy for global elimination of LF.

2. Studies related to disability management in filarial disease: There were four studies under this head that were meant to aid alleviation of the problems associated with the disability caused by LF disease.[7,8, 9,10]

i. A Preliminary study of filariasis related acute adenolymphangitis (ADL) with special reference to precipitating factors and treatment modalities (1991-93). This study was intended to establish the link between ADL and secondary bacterial infection. The conclusion was that the acute attacks of ADL in filariasis associated lymphoedema were precipitated by bacterial infections, especially by Streptococci. The presence of 'entry lesions' for these bacteria in the affected limb and the prevention of such attacks by proper 'foot hygiene' measures were established for the first time.[7]

ii. The next study estimated ASO titer as an indicator of streptococcal infection precipitating acute adenolymphangitis in Brugian lymphatic filariasis (1994-96), which was funded by 'Health Action by People'. This was again to establish the link between ADL and bacterial infection in LF disease. It was concluded that persistently elevated ASO titers in patients with recurrent ADL pointed to the role of streptococcal infection in precipitating ADL causing worsening of lymphoedema[8]

iii. Another disability related study looked at prevention of acute adenolymphangitis in Brugian filariasis by comparison of the efficacy of repeated doses of ivermectin and diethylcarbamazine, each combined with local treatment of the affected limb by the 'foot care' programme (1994-96). This study paved way for further fine-tuning of the 'foot hygiene' programme in LF lymphoedema. It was established that foot care and hygiene combined with appropriate use of local antibiotics or antifungals effectively reduced ADL occurrence. DEC or ivermectin were no better than placebo in preventing ADL.[9]

iv. A double blind placebo controlled study assessed the efficacy of oral penicillin, diethylcarbamazine or local treatment of the affected limb in preventing acute adenolymphangitis in lymphoedema caused by Brugian filariasis (1996-98). The conclusion from this trial was again that'foot care' is important in preventing ADL attacks. In higher grades of edema where foot care wasinadequate there was additional benefit from local or systemic antibiotic use. Antifilarial drugs have no role in the treatment or prevention of ADL.[10]

3. Socio-economic aspects of disability related to filarial disease: This consisted of follow up and interview of subjects from the above (iv) study who were earlier trained in foot hygiene and were not under supervision for at least two years (2000-01). There were three aspects in this study, which specially looked at advocacy of 'foot-care' programme. Issues addressed were:

i. Efficacy and sustainability of foot care

ii. Community acceptance of 'foot care'

iii. Perceptions and practices regarding LF

Conclusions were that 'foot care' is simple, easy to carry out, effective, sustainable and economically feasible. It prevents ADL and thus worsening of lymphoedema and is presently the most cost- effective method alleviating LF disability to a great extent.[11,12] Lymphoedema causes considerable physical, social, marital, psychological and economic consequences[13]

4. **Ultrasonography to detect live adult filarial worms in the lymphatics:** This study was conducted consequent to the reported detection of live adult worm nests in the lymph vessels of the scrotum in adult males with WB infection. We examined post pubertal males who had microfilaraemia, using ultrasound with a 7.5 MHz probe (1998-99). The lymph vessels of the

scrotum and proximal parts of upper and lower limbs were scanned. We could detect 'filarial dance sign' (FDS) (indicating the presence of live adult worm nests) in the scrotal lymph vessels in two males who had microfilaraemia due to WB infection. But adult worms could not be detected in males with *Brugia malayi* microfilaraemia. This was attributed probably to the smaller size of the adult worm nests in BM infection.[14]

But in another recent study at this centre (2004-2008) where we examined children with filarial infection, we could demonstrate the presence of live adult worm nests in the lymph vessels of either inguinal, axillary, epitrochlear or popliteal region. This was made possible because Doppler sonography using 7.5-10MHz probe with Colour-power and pulse-wave Doppler was utilized in this study.[15]

5. Study on pharmacokinetics of DEC and ABZ co-administration: This study was carried out in collaboration with the Pharmacy Dept., University of IOWA, USA (2000-2001). This was the first pharmacokinetic study of DEC and ABZ co- administration. Results indicated that single oral doses of DEC 6 mg/kg and ABZ 400 mg had no influence on the pharmacokinetics and Pharmacodynamics of each other when given concurrently.[16,17]

6. Immunological studies: There were two studies in this group. The first one was conducted in collaboration with London School of Hygiene & Tropical Medicine. The second study was a multi- centric study funded by the ICMR and was done in collaboration with VCRC Pondicherry and PGI Chandigarh.

i. This was to study proteins on sheath of BM mf and also the isotypes of IgG from mf negative patients with chronic disease that reacted with sheath of BM mf (1995). The conclusions were that microfilaria of BM have human IgG on their sheath, but no human albumin. Sera of all mf negative subjects with chronic BM LF contained anti-sheath antibody of IgG2 class that reacted with the sheath of mf from other subjects.[18]

ii. This ICMR multi-centric study was meant to assess Immunological (immunoglobulin and cytokine) responses in BM infections (2001-02). The sera from subjects collected at Alappuzha centre were dispatched to PGI, Chandigarh as part of this study.

7. Diagnostics for Brugia malayi infection: The studies under this head were part of multicentric evaluation of ELISA and 'Brugia rapid' dipstick test to detect filariasis specific IgG4 for BM infection (2000-02). These were carried out as part of TDR/WHO programme in collaboration with Universiti Sains Malaysia. The results showed that both 'Brugia Rapid' dipstick test and ELISA to detect IgG4 antibody using a monoclonal antigen (BmR1) are highly sensitive and specific for BM infection.[19,20,21,22]

8. Wolbachia related study: This was a case study of microfilaraemia of BM /WB /Mixed infections in patients with tuberculosis infection who were being treated under DOTS regime and were to receive rifampicin for 6 months (2002-04). They were observed for one year with periodic assessment of mf counts by Nuclepore membrane filtration. The rationale for this study was that rifampicin was reported to deplete Wolbachia symbionts in the filarial parasite adversely affecting fertility of the worm and thereby depleting the microfilaria in the blood. There were only a very small number of mf positive patients who were under DOTS and because of this, statistically significant conclusions could not be drawn.

9. Study on lymphatic filariasis in children: This is an important cross-sectional study on lymphatic filariasis in children from different areas of Ambalapuzha and Cherthala Taluks endemic for *Brugia malayi* infection (2004-2008). A total of 7934 children between 3-15 years were screened from the field by night blood examination for mf and IgG4 antibody. Out of them 100 children who either had mf in their blood, any clinical or subclinical filarial disease or were positive for filariasis specific IgG4 were enrolled in the study to be followed up for three years. Blood examination for mf, IgG4 test, Doppler Ultrasonography and lymphoscintigraohy were done at enrollment and repeated at every 6 months of follow up. They were administered DEC 6 mg/kg and ABZ 400 mg at enrollment and during follow up visits for three years.[23]

The results of this study brought out many important aspects of filariasis infection and subclinical disease in these children. The most relevant findings from the study were that in *Brugia malayi* infection in children are:

i. The 'filarial dance sign' indicating the presence of live adult worms were detected in the lymph vessels of axilla, inguinal region and occasionally in the popliteal or epitrochlear regions by Doppler sonography.[15]

ii. Subclinical disease characterized by dilatation of lymph vessels was seen by lymphoscintigraphy in children with BM infection even when they did not have any evidence of clinical disease.[24]

iii. DEC + ABZ administration at 6 months interval cleared microfilaraemia in 100%; relieved early lymphoedema in 75%; cleared FDS in 100% and reversed LV dilation in 89.6% .

Conclusions from this study of BM LF in children are:

a. This is the first evidence of reversibility of LF infection, sub clinical and clinical disease in children after administration in drugs in doses recommended for Mass Drug Administration (MDA) in Global Programme for Elimination LF (GPELF)

b. MDA thus has the potential to prevent /reverse LF disease manifestations in the treated communities, especially children, when treated at early stages of infection.

c. These findings have definite impact as an advocacy message for the morbidity control aspect of GPELF.[25,26]

10. ICMR Monograph on Indian medicinal plants used in treatment of lymphatic filariasis: I was chosen by ICMR as the expert in LF, to prepare a Monograph on Indian medicinal plants used in the treatment of lymphatic filariasis and the project was funded by ICMR. This book was meant to include details of all medicinal plants used in LF from different Indian Systems of Medicine namely, Ayurveda, Sidha and Unani. The book was completed in time after collecting the reference material from various institutions, obtaining photographs of all plants and getting necessary help from the experts in different Indian systems of medicine. The manuscript submitted initially was reviewed by ICMR experts. The final version of the Monograph after inclusion of changes suggested by them is submitted to ICMR by the end of 2009, for publication.

Importance of the filariasis research done in this unit:

This centre has been extraordinarily productive during its past 21 years of existence. The research output of the centre has helped to place Alappuzha and the State of Kerala on the lymphatic filariasis map of the world. The research carried out at this centre has helped to formulate many of the strategies that are part of the GPELF. Important contributions of this centre relate to the development of chemotherapeutic tools for the control of Brugian filariasis, management of morbidity associated with lymphatic filariasis and development of newer technologies to understand the pathogenesis of the disease especially in children.[27,28,29]

Over 30 research papers have been published as a result of the work carried out at this centre, in several reputed peer reviewed journals. All these publications have also influenced the formulation of policies of both national and global programmes for the control of lymphatic filariasis.

The activities of this centre have been funded largely by TDR/WHO and ICMR and they have supported research projects by providing both finance as well as other resources. Based on the funding made available to the projects, this unit has been able to create infrastructure that have allowed the upgrading of the facilities at the TD Medical College Hospital.

In view of the importance of the research work done in this unit, I have been involved in many national and international activities concerned with LF. Thus I have been WHO expert for Filariasis from 1990; Executive Committee Member of International Society of Lymphology (1997-2001); Member SAC, RMRC (ICMR), Bhubaneswar (1998); Member, SAC, VCRC Pondicherry(2001); Member task force of ICMR for Filariasis from 1999; Member, WHO South-East Asia Region (SEAR) Progress Review Group for LF Elimination and had been the main resource person for the workshops conducted by NICD, Delhi for the training of district level trainers in LF morbidity management at Regional Filaria Training and Research Centres of NICD. I have been closely associated with the National and State level activities of LF Elimination Programme ever since its inception in 2000. Dr. T.K. Suma, co-investigator of the LF research studies has been designated now as WHO expert for filariasis.

In summary, the Filariasis Chemotherapy Unit of TD Medical College Hospital has played a significant role in continuing research in both clinical and laboratory aspects of lymphatic filariasis and has provided valuable support to GPELF. The activities of the centre have received wholesome praise from both the scientific and lay community for its contributions. Needless to say, the continued support of this centre will enhance the prestige to the Directorate of Medical Education of Government of Kerala and also provide the impetus for carrying out further important research activities in this neglected tropical disease.

END NOTE

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