Chemotherapy of Sputum Positive Pulmonary Tuberculosis
A journey through forty years of its evolution at the Tuberculosis Research Centre

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Summary

The Tuberculosis Research Centre, Chennai, has made significant contributions, in terms of evolution of effective, safe and programme-oriented chemotherapeutic regimens and simple, innovative strategies, for the treatment of sputum-positive pulmonary tuberculosis. Of these, ambulatory domiciliary treatment and supervised intermittent chemotherapy have added a new dimension to tuberculosis control. Of many 12-month regimens evolved by the Centre, a supervised twice-weekly regimen (SHTW) of streptomycin (S) and Isoniazid (H) was most effective (favourable response at the end of chemotherapy 94%, 4-year bacteriological relapse 9%) in drug-sensitive patients. Among short-course regimens, 6-month supervised, intermittent regimens containing rifampicin and isoniazid throughout (supplemented with pyrazinamide and streptomycin or ethambutol for initial two months) were highly effective (unfavourable response at the end of chemotherapy less than 1%, bacteriological relapse about 8%) in drug-sensitive patients and had low drug toxicity. But these regimens failed in patients with initial drug resistance to isoniazid and streptomycin. Prevention of emergence of drug resistance, especially multi-drug resistance, should be the aim of all concerned. This can be achieved by treating new sputum-positive patients with standardised short-course regimens.

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INTRODUCTION

The Tuberculosis Research Centre (TRC), Chennai, (formerly the Tuberculosis Chemotherapy Centre, Madras) has carried out many controlled clinical trials to investigate a variety of drug regimens (both 12-months and short-course) for the treatment of sputum- positive pulmonary tuberculosis. This paper relates to the TRC experience spread over four decades in the evolution of tuberculosis chemotherapy and its impact on the control of the disease.

MATERIALS AND METHODS

Patients

In brief, the patients were aged 12 years or more and had attended chest clinics because of symptoms. They denied history of previous anti-tuberculosis chemotherapy or admitted to have had it for not more than two weeks (but upto six months in one study). They had bacteriologically confirmed pulmonary tuberculosis, with atleast two sputum cultures positive for *Mycobacterium tuberculosis*. During the treatment and follow-up (upto 5 years from the start of treatment) phases, their progress was monitored by sputum examination (supplemented with chest x-ray and biochemical investigations as and when indicted) at specific periodic intervals. The treatment outcome was assessed in terms of favourable or unfavourable response at the end of chemotherapy and bacteriological relapses occurring after stopping chemotherapy.

Definitions of treatment outcome

a) **Favourable response** : A patient was considered to have a favourable response at the end of long-term (12 months) chemotherapy if all sputum specimens collected during the last three months (10,11 and 12) of treatment were all negative by culture for tubercle bacilli or (in a small proportion, about 5% , of patients) if cultures were all negative at three or more consecutive months, but an isolated positive culture occurred at one of the last three (10, 11 or 12) months[1]; and in the case of short-course chemotherapy, if all six sputum specimens collected during the last two months of treatment were culture-negative[2].

b) **Unfavourable response** : A patient was defined to have an unfavourable response[1,2] at the end of chemotherapy (i) if his sputum cultures were never all negative for three consecutive months (applicable for 12 months regimens), OR if he had two or more positive sputum cultures in the last two months of treatment, including atleast one in the last month (in the case of short-course regimens), OR (ii) if he died of tuberculosis, OR (iii) if his treatment was changed for persistent sputum positivity or for deterioration (radiographic or clinical) of his disease.

c) **Bacteriological relapse:** A bacteriological relapse was defined as the occurrence of two or more cultures positive for *M.tuberculosis* in any 6-month period (in the case of long–term chemotherapy)[3], or in any three consecutive months (applicable for short-course chemotherapy)[4,5] after stopping chemotherapy; however, treatment was restarted only if atleast one culture yielded a growth of 20 colonies or more and was associated with atleast one positive smear.

d) **Bacteriological procedures:** Sputum specimens were examined by microscopy and culture. Positive sputum cultures were screened for *M.tuberculosis* by testing with a variety of identification tests and drug susceptibility tests (DST)

Definitions of drug resistance

Resistance to streptomycin[6, 7] was defined as a resistance ratio (RR) of 8 or more. A minimal inhibitory concentration (MIC) of 1 mg/l or more and of 128 mg/l were defined as resistance for isoniazid [7, 8, 9] and rifampicin [7, 10] respectively.

RESULTS

Twelve-month primary chemotherapy regimens

For two decades since the 1950s, the TRC had treated more than 2000 sputum positive (drug – sensitive) patients with a variety of 12-month regimens containing isoniazid (H), in combination with PAS (P) or thioacetazone (T) or ethambutol (E) or streptomycin (S). Of many studies on 12-month regimens, the most outstanding was a concurrent comparison of home and sanatorium treatment or "The Madras Study". In brief, 163 sputum - positive (drug-sensitive) patients were treated by random allocation, either in a sanatorium (81 patients) or in their homes (82 patients) All of them received daily isoniazid plus PAS (PH) for one year. The home patients were treated on an ambulatory, out-patient basis and they self-administered the drugs collected by them; the sanatorium patients swallowed the drugs in the presence of nursing staff.

The main findings, in brief, were as follows:

Ambulatory domiciliary treatment of sputum positive patients was very effective despite adverse circumstances (ill-ventilated overcrowded homes, poor diet, strenuous physical activity) [11, 4], was safe and did not expose the family contacts to any special risk of contracting the disease from the infectious patient[12], disruption of family life resulting in serious marital problems was minimal[11], and was considerably cheaper (by about 15 times) than sanatorium treatment[13]. This study clearly established that effective chemotherapy practiced in a well-organized out-patient clinic and prolonged cooperation by the patient were the keys to the treatment success.

The results of this epoch-making study thoroughly revolutionized the concept of tuberculosis control globally. Strongly recommended by the WHO[14], ambulatory domiciliary chemotherapy became the prime tool of tuberculosis control in India and elsewhere.

Besides the isoniazid – PAS (PH) regimen, the centre has evolved two other 12-month daily regimes (Table 1) containing isoniazid and either thioacetazone[15] or ethambutol[16,17].

The daily oral drugs are normally supplied to the patient for self-administration by him. Occasionally, he might collect the drugs regularly but fail to consume them (concealed irregularity). This problem could be detected if his progress during chemotherapy is

monitored by sputum culture and drug sensitivity tests (a procedure not practised under programme conditions). The repeated occurrence of isoniazid –sensitive bacilli could offer a clue. It was observed[18,19] that under routine treatment programmes about 35% to 45% of patients still had isoniazid-sensitive bacilli at the end of a year's chemotherapy with INH-PAS or INH- thioacetazone. In contrast, a TRC study[1] showed that 52 of 53 (virtually 100%) culture-positive patients at one year had isoniazid-resistant bacilli under controlled trial conditions. These findings strongly suggest that patients, who continue to excrete isoniazid-sensitive bacilli after a year's chemotherapy with isoniazid-containing regimens, most probably consume the drug irregularly.

Supervised therapy is the best way of ensuring drug consumption by the patient. Since daily supervision is impracticable, the centre evolved intermittent (twice-weekly) regimens. The scientific rationale for intermittency was provided by the centre's study on the efficacies of different dosages of isoniazid. This study [1,20] showed that if the daily dosage of isoniazid was 400 mg for a patient weighing 45.4 kg, (about 9 mg/kg), the response was better if the drug was given in a single dose of 400 mg than when it was given in two divided doses each of 200mg. It was observed that the response to treatment was related to the peak serum isoniazid concentration; and it was higher when 400mg of isoniazid was given in one dose than in two divided doses each of 200mg.These findings suggested that large doses of isoniazid, despite gaps between the doses, would still be effective.

Animal experiments showed that streptomycin and isoniazid were well suited for intermittency. Streptomycin maintained its bactericidal activity even when the interval between doses was upto eight days[21,22]. Isoniazid in high doses was effective when the interval between doses was two or three days, but its efficacy dropped considerably when the interval was eight days[23].

On the basis of above-mentioned sound scientific basis, the TRC evolved a 12-month supervised twice-weekly regimen (SHTW) consisting of streptomycin (1g) and isoniazid (14mg/kg). This regimen had a favourable response rate of 94% at one year and a 4-year

relapse rate of 9%[17] among initially drug-sensitive patients. Furthermore, its efficacy was uninfluenced by the isoniazid inactivation status of the patient; it was highly effective in both slow and rapid inactivators of isoniazid, a favourable response occurring in 97% and 91% of patients respectively[24]. The concept and genesis of supervised chemotherapy was a major breakthrough in the evolution of tuberculosis chemotherapy. Moreover, the current trend in tuberculosis control, namely the DOTS strategy revolves around supervised treatment, now known as directly observed treatment.

A field study at Bangalore[25] reported that one-fourth of the patients refused SHTW regimen at start because of rigid working hours or distance between the home and the clinic; another one-fourth received 80% or more of due drugs in one year and 68% had negative cultures at the end of chemotherapy. In this context, the success story of a community-based tuberculosis chemotherapy programme practised in Czechoslovakia is worth mentioning. In brief, this programme[26] was patient – friendly, flexible and designed in such a manner that there would be minimal disruption of his normal activity and enable the patient to continue his treatment (SHTW) for one year without interruption. The result was astounding; all 233 (100%) patients had a successful outcome. In short, the Czech experience should serve as a model to all treatment providers. Therefore, Toman[27] advocated strongly that supervised intermittent chemotherapy should always be considered for sputum – positive patients and emphasized that the treatment programme must be flexible and acceptable to the patients.

The centre has also evolved 12-month fully oral twice-weekly regimens containing isoniazid and either PAS or ethambutol (Table 1); the efficacy of each regimen was about 90%[16,28]. Since once-a-week attendance would be convenient to the patient, the centre attempted to evolve effective once-weekly regimens of streptomycin and isoniazid (SHOW) or of ethambutol and isoniazid (EHOW). The proportion of patients with a favourable response at one year were low in both regimens (SHOW 68%, EHOW 75%)[6,16]. The reason for the poor efficacy was attributable to the isoniazid inactivation status of the patient. The favourable response was substantially lower in the rapid inactivators (SHOW 56%, EHOW 57%) than in slow inactivators (SHOW 76%, EHOW

91%) of isoniazid[6,16]. Attempts to boost their efficacies in rapid inactivators failed in the case SHOW [24], but succeeded in EHOW[16].

The various TRC 12-month regimens (daily and intermittent) and their efficacies are presented in Table 1. With the advent of short-course chemotherapy, these regimens have become obsolete in many countries.

Twelve-month "reserve" regimens

Some drug-sensitive patients failed on primary chemotherapy with 12-month regimens and developed acquired drug resistance to one or more drugs. They were retreated with combinations of cycloserine ethionamide, pyrazinamide and ethambutol ("reserve" drugs). The findings of two important studies are summarized here. Of a group of 51 patients, with bacilli resistant to isoniazid (including 80% with streptomycin-resistance) treated with a 12-month daily regimen of cycloserine, ethionamide and pyrazinamide [29]. 73% had a favourable response at one year. Of another group of 57 patients with bacilli resistant to streptomycin and isoniazid, but sensitive to rifampicin, treated with a 12-month thrice-weekly regimen of ethambutol and rifampicin supplemented with kanamycin for initial three months [30]91% had a favourable response.

Short Course Chemotherapy (SCC)

Treatment default with the erstwhile 12-month regimens under programme conditions was the main reason for the failure of mass domiciliary chemotherapy. During the 1970s / 1980s only about 27% to 35% of patients in India treated with 12-month regimens completed the treatment in the scheduled time[31,32,33]. This problem was observed elsewhere also; only 28% to 35% of patients in Kenya or in Tanzania completed one year treatment[34,35]. It was believed that shortening the duration of chemotherapy substantially could promote patient compliance.

The TRC has investigated a variety of short-course regimens (Table 2) of 3 to 8 months' duration. The majority were of 6 months' duration, were fully intermittent and all, but one ($2SHRZ_3$or$2SHRZ_2/4SH_2$) contained rifampicin for entire 6 months and all but one

($2HRZ_2/4HR_2$) had four bactericidal drugs for two months initially; none of them contained quinolones.

Efficacy in initially drug-sensitive patients

Of more than 3500 drug –sensitive patients, treated with the TRC short-course regimens, (data not tabulated), only one regimen, a 6-month non-ethambutol twice-weekly rifampicin regimen ($2HRZ_2/4HR_2$) had maximum number of patients with an unfavourable response at the end of chemotherapy, namely 24 of 257 (9.3%) patients[2]. The remaining regimens had low failures during chemotherapy ranging from 0% to 4%.

Considering bacteriological relapses among drug-sensitive patients (Table 2), three regimens, namely a 5-month ($3SHRZ/2SHZ_2$) a 7-month ($2SHRZ/5SHZ_2$) and an 8-month (2EHRZ/6EH) regimens had low relapses rates of 4% to 5% [5,4,2] .Furthermore, two regimens a 3-month (3SHRZ) and a 5-month non-rifampicin ($3SHZ/2SHZ_2$) regimens had high relapse rates of 16.8% and 20.0% respectively[5]. The 6-month intermittent regimens, containing rifampicin throughout had relapse rates of about 6 to 11%[36,37,2] .

Efficacy in patients with initial drug resistance

Analyses of data showed that the results in patients with initially drug-resistant bacilli treated with TRC short-course regimens was independent of the duration of the regimen. Therefore, the response is presented in Table 3 according to the duration and rhythm of administration of rifampicin[38].

An unfavourable response occurred in 40% of 30 patients with initial INH-resistance and in 70% of 30 patients having double-drug (SH) resistance at start, when rifampicin was not given. The proportions dropped significantly in both categories, when rifampicin was given daily for initial 2 or 3 months, to 8% of 52 ($p< 0.0001$) and to 17% of 46 ($p< 0.0001$) respectively. A similar finding was observed when the drug was given intermittently for 6 months, an unfavourable response occurring in 11% of 74 ($p< 0.0001$) former patients and in 26% of 91 ($p< 0.0001$) latter patients. It was also observed especially in double-drug

resistance that the occurrence of an unfavourable response was considerably less when rifampicin was given daily for 2 or 3 months than when given intermittently for 2 months, the proportions being 17% of 46 and 70% of 33 respectively. These findings suggest that the duration and probably the rhythm of administration of rifampicin influenced the treatment response in initially drug-resistant patients.

Besides the above-mentioned regimens which contained streptomycin (in addition to rifampicin and isoniazid); the centre investigated fully oral regimens[2,37]. Of these, a 6-month twice-weekly non-ethambutol regimen($2HRZ_2$/ $4HR_2$) was ineffective in patients with initial INH-resistance, an unfavourable response occurring in 62% of 74 patients; but this proportion dropped significantly ($p< 0.0001$) to 20% of 59 patients when the regimen was strengthened by ethambutol throughout ($2EHRZ_2/4EHR_2$). An 8month daily regimen containing rifampicin for initial 2months (2EHRZ/6EH) and a 6-month rifampicin regimen having a thrice-weekly phase for initial 2 months ($2REHZ_3/4RH_2$) had unfavourable response rates of 17% and 25% respectively.

SCC failures with multiple drug resistance (MDR TB)

There were drug-sensitive patients who failed during SCC therapy and developed resistance to both rifampicin and isoniazid (Multiple Drug Resistance – MDR TB). They were retreated with appropriate drugs not received by them so far[39]. Even with individually tailored regimens, the success rate was only 50% and the mortality rate was 34%.

Ultra-short regimens

Short-course regimens of less than 6 months' duration would be convenient for both patients and treatment providers. The TRC is currently investigating fully oral regimens of 3 to 5 months' duration. This study[40] showed that 4 or 5 month regimens that contain four bactericidal drugs (ofloxacin, isoniazid, rifampicin and pyrazinamide) for atleast three months initially would be effective (more than 95%) in new smear-positive patients without causing significant adverse reactions. It is emphasized that two months of initial

intensive phase is inadequate for sterilizing the bacterial load. The encouraging results have led to the next trial on efficacy of 4-month intermittent regimens.

Low emergence of rifampicin resistance

A TRC study[41] reported that the emergence of resistance to isoniazid, rifampicin or both drugs occurred in only 1% of 1435 patients with drug-sensitive bacilli initially and in 11% of 320 patients with bacilli initially resistant to isoniazid when treated with standardized short-course regimens. Moreover, the overall emergence of rifampicin resistance occurred in only 2% of all 1755 patients. Thus, standardized short-course treatment carries a minimal risk of emergence of rifampicin resistance

SCC under programme conditions

Encouraged by excellent treatment results of 6-9 month regimens in clinical trials, the Government of India carried out a field study (through the TRC) on the feasibility and acceptability of SCC in 18 districts[42] of India under the then existing programme conditions. Adult new sputum smear-positive patients were offered treatment with one of three 6 to 8 month short-course regimens. This study showed that under programme conditions efficiencies of case-finding, case-holding and chemotherapy (short-course) were 41%, 54% and 100% respectively. In such a situation, the overall impact of the programme was estimated be around 22%. In order to achieve a significant impact on the control programme case finding and case-holding activities have to be augmented.

DOTS strategy

The Tamil Nadu Government implemented the Directly Observed Treatment Short-course (DOTS) Strategy in Thiruvallur District in 1999. The TRC carried out a series of studies to assess the performance of DOTS under programme conditions. The findings were briefly as follows. Of 295 new smear-positive cases (Category I) treated with a 6-month regimen ($2H_3R_3Z_3E_3$ / $4H_3R_3$) 74% were cured, 17% defaulted 5% died and 4% failed[43]. It was concluded that the high defaulter rate was programme-related and needed corrective measures to ensure patient's convenience. And of another 503 new smear-

positive patients (Category I) cured after SCC ($2H_3R_3Z_3E_3/4H_3R_3$) and followed up for 18 months, 62 (12%) relapsed; 48 of 62 (77%) relapsed during the first 6 months of follow up [44]. The relapse rate was higher in patients who were irregular for treatment (20%) than in those who were regular (9%) ($p<0.0001$). It was concluded that the relapse rate could be reduced by proper counselling. The influence of initial drug susceptibility pattern on the treatment outcome was studied in 431 re-treatment (Category II) cases [45]. The treatment outcome was successful in 41% of 254 patients with fully sensitive bacilli, in 40% of 128 patients with bacilli resistant to drugs other than isoniazid and rifampicin and in 27% of 49 with MDR TB. The defaulter rate among them ranged from 38% to 46% and was high among males, smokers and alcoholics. It was concluded that these patients need to be targeted with additional health education and intensive counseling. Finally the administrative and technical issues, vital for a well-functioning programme[46] were regular availability of essential staff, regular supervisory visits and review meetings.

DISCUSSION

The importance of two outstanding achievements of the TRC namely, the ambulatory domicilary chemotherapy and the supervised intermittent chemotherapy is eroded by disturbing trends in technically advanced countries.

Considering the first item, despite the knowledge that sanatorium treatment is not superior to home treatment many countries, including UK, admit the tuberculosis patients initially for various flimsy reasons namely investigation or routine policy[47,48]. Stranger still is the trend that in many countries (example: Czechoslovakia) it is still a normal practice to treat their tuberculosis patients in sanatorium or hospitals for many months [26].

Nevertheless, hospital treatment might indeed, be necessary in the treatment of MDR-TB patients because of the complexity of management, including pulmonary surgery[49] where-ever possible. It is not surprising therefore that the success rate in the treatment of these patients under DOTS strategy in India was of the order of only 17 to 27% [45,50]. Moreover, it is expected that there could be an increase in the number of MDR TB

patients in our country in the years ahead because of a predicted rise of HIV-positive individuals.

Regarding the supervised intermittent chemotherapy, it is scarcely prescribed in UK; only 7 of more than 300 physicians prescribed it for just 2% of more than 1200 new cases [47]. More puzzling is that this treatment was not prescribed even for alcoholics or elderly patients in whom self-administrated chemotherapy was bound to fail [47,51]. Indeed, none of 449 doctors (including 213 chest specialists) in Lucknow prescribed this WHO-recommended treatment [52].

The centre has investigated a variety of non-quinolone regimens of 3 to 8 months' duration. Of these three were ineffective even in initially drug-sensitive patients, because of high unfavourable response (9.3% in $2HRZ_2/4HR_2$)[2] or high relapse rates of (16.8% in 3SHRZ; 20.0% in $3SHZ/2SHZ_2$)[5]. The remaining regimens were effective in initially drug-sensitive patients; but of them, regimens that contained rifampicin, isoniazid and pyrazinamide daily for initial 2 or 3 months had high levels of hepatitis (4% to 8%) or arthralgia (24 to 43%)[2,10,53].

The 6-month intermittent regimens containing rifampicin throughout with or without ethambutol and having an initial intensive phase two months, were not only very effective in drug-sensitive patients but also had low drug toxicity[2,36,37,54]. They had an unfavourable response of less than 1% and a bacteriological relapse in about 8% of more than 1000 drug-sensitive patients. The incidence of hepatitis was 0.2 to 2% and that of arthralgia was 3 to 13%. But these regimens were not very effective in initially drug-resistant patients[2,37,38].

A Hong Kong study[55] showed that 6-month thrice-weekly regimens containing 4 drugs (rifampicin, isoniazid, pyrazinamide and ethambutol or streptomycin) were highly effective even in patients with initial double-drug (streptomycin and isoniazid) resistance and had low level of drug toxicity. It may not be feasible in our country to give 4 drugs for entire 6 months. The alternative is a 6 month thrice-weekly oral regimen containing

rifampicin (R) isoniazid (H) , pyrazinamide (Z) and ethambutol (E) for initial 2 months, followed by rifampicin (R), Isoniazid (H) for next 4 months ($2HRZE_3$ / $4HR_3$). This regimen would be adequate in new smear-positive patients because 72-85% of new sputum-positive patients under DOTS programme in South India have bacilli sensitive to the three drugs isoniazid, rifampicin and streptomycin [56,57].

The above-mentioned regimen, however would be inadequate for previously treated patients, in whom the level of initial drug resistance could be high. Studies carried out at Thiruvallur[56] and Bangalore[50] showed that among previously treated (Category II) patients the occurrence of initial resistance to one or more drugs was 40-41%; overall resistance to H 27-37%, to R12-16%, and to HR12-13%. A TRC study[2] showed that in patients with initial INH-resistance, an unfavourable response occurred in significantly less ($p<0.0001$) proportions of patients treated with a 6-month rifampicin regimen which also contained ethambutol than in those treated with a 6-month rifampicin regimen but without ethambutol, the proportions being 20% of 59 and 62% of 74 patients respectively. The other observation that initial SH-resistance among previously treated patients in South India was only about 12%[50,56], suggests that streptomycin could still be beneficial. On the basis of the above knowledge, it is hoped that an 8-month thrice-weekly regimen containing isoniazid, rifampicin and ethambutol throughout (supplemented by streptomycin and pyrazinamide) for initial 3 months ($3HRZES_3$ / $5HRE_3$) should be effective in already treated patients without MDR TB.

The TRC experience in the treatment of MDRTB patients has been unsatisfactory so far. The success rate was only 50% despite treatment with individually tailored regimens[39]. Studies elsewhere showed that the management is extremely difficult and required prolonged treatment (18 to 36 months) with poorly tolerated, toxic and costly drugs combined with pulmonary surgery wherever possible [49]. The emergence of multiple drug resistance is largely man-made and due to faulty drug therapy. A Lucknow study[52] involving 449 allopathic doctors (including 213 chest specialists) reported that about 75% of them (including chest specialists) erred with respect to treatment duration or drug dosages or both. Rifampicin was misprescribed by about 27% of doctors. In addition,

only 55% used NTP/ WHO conforming regimens. This problem occurred in Britain also where only 53% of the patients were treated with regimens recommended by the British Thoracic Association[47]; moreover, only 6% of patients received pyrazinamide[47]. The only way to minimize the emergence of multi-drug resistance[41] is by curing large numbers of drug-sensitive patients by using standardized short-course regimens under DOTS strategy.

The DOTS programme, implemented in India during 1999, has produced remarkable clinical[58] and epidemiological[59] results. The treatment success rate of smear-positive cases doubled (40% before and 80% after DOTS); and the death rate became one-seventh (29% before and 4% after DOTS)[58]. A longitudinal study in Tiruvallur area (South India)[59] reported that during a 30-year period prior to DOTS , the annual decline in the prevalence of culture-positive and smear-positive cases were 2.3% and 2.5% respectively. During a 2.5 year DOTS period, the rates increased in both categories, to 11.9% and 5.6% respectively. The DOTS period accounted for one-fourth of the decline in the prevalence of culture-positives observed over entire 33 years. If these trends continue in the future, we could expect a substantial reduction of the disease burden unless some other factor (example: HIV infection) sets in.

Limitation

The TRC data presented in this review article were all observed under controlled clinical trial conditions. These need not be true under day-to-day programme conditions. However, the data pertaining to the field studies relate to operational studies monitored by the Centre.

CONCLUSION

The contribution by the TRC towards the evolution of chemotherapy of sputum-positive pulmonary tuberculosis has been monumental, of which ambulatory domiciliary chemotherapy and supervised chemotherapy (Directly Observed Treatment) are the most

outstanding. If and when the disease is eradicated from our country, the posterity will fondly remember this Centre.

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Table 1: Efficacies of TRC 12-month daily or intermittent (twice or once –weekly) regimens in patients with drug-sensitive bacilli initially.

Regimen	Rhythm of administration	Efficacy		Reference
		Favourable response at one year %	Bacteriological relapse in 4-year follow-up %	
INH + PAS	Daily	85	17	17
INH + Thioacetazone	Daily	82	19	17
INH + Ethambutol	Daily	96	15	16
INH + SM	Twice-weekly	94	9	17
INH + PAS	Twice-weekly	88	-	28
INH + Ethambutol	Twice-weekly	88	26	16
INH + SM	Once-weekly	68	19	6,17
INH + Ethambutol	Once-weekly	75	54	16

Table 2: Bacteriological relapses requiring treatment in drug-sensitive patients treated with TRC short –course regimens

Serial Number	Duration (Months)		Regimen	No. of patients assessed	Relapse during follow up of 53-57 months (%)	Reference
	Reg	Rif				
1	3	3	3SHRZ	113	16.8	5
2	5	0	$3SHZ/2SHZ_2$	115	20.0	5
3	5	2	$2SHRZ/3SHZ_2$	126	7.1	4
4	5	3	$3SHRZ/2SHZ_2$	97	5.2	5
5	6	2	$2SHRZ_3$ or$2SHRZ_2$ /$4SH_2$	184	9.2	36
6	”	6	$2SHRZ_3/4SRH_2$ or $4RH_2$	184	6.5	36
7	”	6	$2SHRZ_3/4SRH_1$ or $4RH_1$	195	5.6	36
8	”	6	$2SHRZ_2/4SRH_2$ or $4RH_2$	179	7.3	36
9	”	6	$2SHRZ_2/4SRH_1$ or $4RH_1$	195	6.7	36
10	”	6	$2EHRZ_2/4EHR_2$	258	10.9*	2
11	”	6	$2HRZ_2/4HR_2$	229	9.6*	2
12	”	6	$2REHZ_3/4RH_2$	269	8.9	37
13	7	0	$2SHZ/5SHZ_2$	253	6.7	4
14	7	2	$2SHRZ/5SHZ_2$	124	4.0	4
15	8	2	2EHRZ/6EH	290	5.1*	2

* Follow-up ; 16-18 months
S=Streptomycin; H = Isoniazid ; R=Rifampicin; Z=Pyrazinamide; E=Ethambutol

The number before the alphabets denotes the duration (in months) of the drug combination. The subscript number after the alphabet indicates the number of doses per week of the drug combination. Absence of subscript number means that the drug combination is given daily.

Table 3: Unfavourable response at the end of chemotherapy in patients with initially drug resistant bacilli related to the duration and rhythm of administration of rifampicin*

Initial resistance to	Rifampicin		Number of patients assessed	Unfavourable Response %
	Duration (Months)	Rhythm of administration		
Isoniazid only (n=175)	0	-	30	40
	2	Intermittent	19	26●
	2 or 3@	Daily	52	8
	6	Intermittent	74	11
Streptomycin and Isoniazid (n=200)	0	-	30	70
	2	Intermittent	33	70
	2 or 3@	Daily	46	17
	6	Intermittent	91	26

* : Reference 38

● Percentage based on less than 25 observations

@ Number of patients small on splitting.