Nigerian Journal of Clinical Practice
December 2001, Vol. 4 (2); 59–63

TREATMENT OF PULMONARY TUBERCULOSIS: AN ASSESSMENT OF THE EIGHT MONTH REGIMEN RECOMMENDED BY THE NIGERIAN NATIONAL TUBERCULOSIS CONTROL PROGRAMME COMMITTEE FOR NEWLY DIAGNOSED CASES USING DIRECTLY OBSERVED TREATMENT SHORT-COURSE IN 500 SUBJECTS IN IWO, NIGERIA: A CONTROLLED CLINICAL TRIAL.

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ABSTRACT

A clinical study was carried out between January 1996 and December 1997 in Iwo, Osun State of Nigeria to determine, among others, the effectiveness of the 8 - month regimen recommended by the Nigerian tuberculosis control programme committee (NTCP). This involved the use of ethambutol (ETH), rifampicin (RMP), Pyrazinamide (PZA) and isoniazid (INH) for the first 2 months by directly observed treatment (DOT) followed by isoniazid and thiacetazone in group one (n=500) or rifampicin in group 2 (n=50). The clinical outcomes were then compared in both. The clinical outcome in terms of the time of sputum conversion, prognosis, radiological changes at the end of treatments and side-effects of the anti-TB drugs were good and confirmed the effectiveness of both regimen. A study of the statistical significance level using x^2 (P>0.01) showed no significant difference in the clinical outcome of the two groups using the prognosis, side-effects profile, sputum conversion and radiological clearance at the end of chemotherapy. The regimen recommended by the Nigerian NTCP is good, effective and is characterised by low and minor side-effects and compare favourably with the 6-month regimen.

KEYWORD: ***Newly diagnosed, pulmonary tuberculosis, national tuberculosis control programme, recommended regimen.***

INTRODUCTION

Despite Global efforts that have been intensified greatly, especially over the past decade, the incidence of tuberculosis is increasing, with more than 1.7 billion people currently infected with Mycobacterium tuberculosis worldwide[1]. The dimension of the problem is largest in sub-Saharan Africa and South East Asia[1,2,3]. Current annual estimates suggest that 9 million new cases of tuberculosis and 3 million tuberculosis deaths occur globally[4]. Over a quarter of a million cases of tuberculosis may be present in Nigeria[5].

We have known for over 100 years that Mycobacterium tuberculosis causes TB. We have had effective anti-TB drugs for nearly 50 years. Yet the world's TB problem is now bigger than ever. The problem is not lack of an effective treatment but that of properly applied short-course chemotherapy (SCC). The World Health Organisation (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD) have recommended directly observed treatment shortcourse (DOTS)[6] for the global control of tuberculosis. Each country is to identify, based on local information, the combination of drugs to be used for the DOTS. Nigeria NTCP has adopted the SCC for treatment of tuberculosis[5], whereby four drugs are used in the initial intensive phase of two months, followed by a continuation phase with two drugs daily for six months in line with the recommendations of WHO and IUATLD (Figure 1 and Table 1).

The aim of the study therefore, is to apply the recommended regimen of the Nigerian NTCP[5], to newly diagnosed (ND) pulmonary tuberculosis (PTB) subjects seen in Iwo, Osun State of Nigeria (group one) and compare same with the six month regimen (group2) and note the effectiveness or otherwise of this regimen.

STUDY POPULATION AND METHODS

A clinical study was carried out between January 1996 and December 1997 to determine the pattern of PTB and the effectiveness of the regimen recommended by the Nigerian NTCP (Figure 1, Table lb) in the ND PTB subjects using DOTS in Iwo Osun State of Nigeria[7]. Nigeria is the largest single geographic unit in the West coast of Africa. Nigeria is located between latitude 4°N and 14°N and between longitudes 3°E and 15°E. It has an area of 923,800 square kilometers and therefore constitute 14 percent of the land area of West Africa. It has a population of 100 - 120 million. It is divided into 36 States with Abuja as the Federal Capital. Iwo where the study was carried out is the headquarters of Iwo Local

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Government Council of Osun State and is 45 kilometers from Oshogbo and Ibadan both are capitals of Osun and Oyo States respectively. Iwo is a rich agricultural area and are mainly Yorubas by tribe. The subjects used were male and female Nigerians aged 15 years and above residing at Iwo. The selected subjects were the patients that presented randomly at Alaye TB control clinic at Iwo with symptoms suggestive of TB and that met the eligibility criteria till the target study size was met. Subjects were eligible if, apart from being symptomatic of TB for at least 6 weeks, (see Table la), Acid and Alcohol fast bacilli (AFB) was demonstrated in their sputum by direct sputum smear using Ziehl-Neelson stain at least two times in line with WHO recommendations[8].

Drugs were provided free by Damien Foundation of Belgium based in Ibadan and is according to the recommendation of the Nigerian NTCP (Table lb and Figure 1). There were two groups, the first group were 500 while the other were 50. The 500 subjects were treated with the 8 - month regimen while the 50 in group two had the 6-month regimen. All the subjects in both groups were treated with the directly observed treatment (DOT) during the initial TB intensive phase and were therefore seen daily.

Home visitors visited all patients that were absent from the clinic (register was kept and marked daily for all patients on the study list by the TB supervisor). He did this Default Tracing Visit (DTV) with the Motorcycle provided and maintained by the Damien Foundation. Drugs were then administered at home for the day of default and family counselling done.

Detailed history, physical examination and laboratory tests (see Table lc & ld) were done for each patient. There were no physical findings on examination in 30 percent of patients seen in both groups. Those with positive physical findings had reduced air entrance to the lungs, dull percussion note over the affected lung zones, scattered crepitations and 5 had bronchial breath sounds in group 1. Side-effects of the anti-TB drugs were specifically sought during visits and this was compared in the two groups including sputum conversion, prognosis and radiological changes observed at the end of treatments. Most of the patients lived at walking distances from the TB control clinic, the longest distance from their homes to the clinic was 10 kilometers.

RESULTS

65 (13%) of group 1 and 7 (14%) of group 2 had a number of minor side-effects of the anti-TB medications (Table 2). The side-effects were mild and did not lead to major change of the anti-TB drugs. Sputum conversion was similar with 100% conversion achieved by the third month in both groups (Table 3). The prognosis is as shown in Table 4 and were similar in both groups. The radiological clearance in 100 (in gp one) and 50 (in group 2) that had the chest x-ray done is as shown in Table 5 and the observations were again similar. The exact radiological findings in these patients included evidence of fibrosis, cavitating lesions, fluffy exudative changes and 5 in group 1, had the destroyed lung syndrome.

Table l(a): **Prevalence of symptoms among 500 ND PTB cases in Iwo Nigeria.**

SYMPTOMS	NO OF CASES AND (%)	
	Group 1	Group 2
Cough	500(100)	50(100)
Sputum production	500(100)	50(100)
Haemoptysis	130(26)	10(20)
Chest wall pain	460 (92)	50(100)
Dyspnoea	130(26)	10(20)
Localised wheeze	70(14)	5(10)
Fever	470(94)	50(100)
Day sweating	20(4)	5(10)
Night sweating	420(84)	50(100)
Loss of weight	470(94)	50(100)
Lassitude (general malaise)	190(38)	10(20)
Anorexia	110(22)	10(20)
Dyspepsia	40(8)	5(10)
Fatigue (weakness)	420(84)	40(80)
Headache	420(84)	40(80)
Palpitation on exertion	140(28)	15(30)
Amenorrhea (women) without pregnancy	10(2)	0(0)
TOTAL	**500(100)**	**50(100)**

Table l(b): **Drugs used for newly diagnosed cases of PTB by dosage, duration and mode of administration as recommended by the Nigerian National tuberculosis control programme committee (NTCP).**

Drugs	Dose	Duration	Mode
	Initial Intensive Phase (Groups 1 & 2)		
1. Ethambutol (E)	25 mg/kg(daily)	2 months	Directly
2. Rifampicin (R)	10 mg/kg(daily)	2 months	Observed
3. Isoniazid (H)	7.5 mg/kg (daily)	2 months	Therapy
4. Pyrazinamide (Z)	30 mg/kg (daily)	2 months	
	Continuation Phase		
(Group 1)			
1. Isoniazid (H)	7.5 mg/kg (daily)	6 months	
2. Thiacetazone (T)	150 mg/day	6 months	
OR (Group 2)			
1. Isoniazid (H)	7.5 mg/kg (daily)	4 months	
2. Rifampicin (R)	10 mg/kg (daily)	4 months	

Table lc (i): **Laboratory parameters in PTB patients. Average PCV per month.**

Month	*Average PCV per month %*	
	Group 1	**Group 2**
0	28	28
1	30	31
2	32	33
3	34	35
5	36	37
8 for group 1 6 for group 2	38	38

Table 1 c (ii): **Average WBC per month**

Month	**Average WBC per month (x109/L)**	
	Group 1	**Group 2**
0	3.5	3.5
1	3.6	37
2	3.8	3.8
3	4	4
5	4.8	5.0
8 for group 1 & 6 for group 2	5.5	5.6

Table lc (iii): **Average ESR per month**

Month	**Male (mm/hr)**		**Female (mm/hr)**	
	Group 1	**Group2**	**Group 1**	**group2**
O	20	22	42	45
1	20	18	38	40
2	18	15	32	35
3	15	14	28	30
5	12	14	22	25
8 for Group 1 & 6 for group2	10	11	20.	18

Table 1(d): **Weight increment pattern before, during and at the completion of treatments.**

Months	**Average weight in kg.**	
	Group 1	**Group 2**
0	46.0	46.0
1	46.8	47.0
2	48.6	49.0
3	49.4	49.5
5	50.7	50.5
8 for group 1 ~ 6 for group 2	50.8	50.9

FIG. 1: **Guidelines for tuberculosis chemotherapy short course chemotherapy for TB patients who have never been treated before regimen and drug dosage for adult.**

Drugs	**Treatment Weight**		
Daily for 2 months	**50 kg and more**	**33-49 kg**	**Less than 33kg**
Ethambutol 400 mg	3	3	2
Isoniazid 100 mg	4	3	2
Rifampicin 150 mg Combined tablet			
Pyrazinamide 400 mg tablet	4	3	2
Daily for 6 months Isoniazid 300 mg			
Thiacetazone 150 mg combined tablet	1	1	2 tablets Isomazid 100mg Thiacetazone 50mg Combined

NB: (a) Drugs in the initial intensive phase of 2 months must be given on an empty stomach in a single dose under strict supervision by a member of staff.

(b) If the sputum smear is positive at the end of 2 months, the intensive treatment should be continued for another month making a maximum of 3 months.

(c) If the intensive phase has been prolonged by 1 month, the continuation phase should last for 5 months.

SOURCE: NIGERIAN FEDERAL MINISTRY OF HEALTH, NATIONAL TUBERCULOSIS CONTROL PROGRAMME (NTCP)

Table 2: **Types and frequency of side-effects of anti-tuberculous drugs used in 500 (group 1) and 50 (group 2) newly diagonised cases of PTB in Iwo Nigeria.**

Type of side-effects	No of cases and (%) group 1 (n=500)	No of cases and (%) group 2 (n=50)
Steven Johnson's syndrome	0(0)	0(0)
Maculopapular rash	2(0.4)	0(0)
Pruritus only	10(2.0)	1(2)
Exfoliative dermatitis	0(0)	0(0)
Fever	10(2.0)	1(2)
Systemic flu-like syndrome (Common cold)	10(2.0)	2(4)
Dizziness	0(0)	0(0)
Tinnitus	0(0)	0(0)
Impared hearing	0(0)	0(0)
Permanent deafness	0(0)	0(0)
Opthalmological (optic Neuritis)	0(0)	0(0)
Gastroenteritis (nausea and vomiting)	8(1.6)	0(0)
Neuropathic (peripheral neuropathy)	0(0)	0(0)
Jaundice (Hepatic)	5(1.0)	1(2)
Thrombocytopenia (Hematological)	0(0)	0(0)
Renal failure	0(0)	0(0)
Arthralgia (Joint pains)	20(4.0)	2(4)
No of cases with side-effects	65(13.0)	7(14)
Total	**500(100)**	**50(100)**

Table 3: **Sputum Conversion during treatment in 500 (group 1) and 50 (group 2) ND PTB cases in Iwo, Nigeria**

Sputum conversion. Months after commencement of treatment	No of cases and (%) Group One	No of cases and (%) Group Two
One	350(70)	35(70)
Two	498(99.6)	49(98)
Three	500(100)	50(100)
Five	500(100)	50(100)
Eight (in group 1) Six (group 2)	500(100)	50(100)
Total	**500(100)**	**50(100)**

Table 4: **Prognosis of 500 (group 1) and 50 (group 2) ND PTB cases after the completion of treatment in Iwo, Nigeria.**

Prognosis	Group One No of cases and (%)	Group Two No of cases and (%)
Death (D)	0(0)	0(0)
Cured and Treatment complete	500(100)	50(100)
(c)		
Defaulted (DF)	0(0)	0(0)
Failure (F)	o(o)	
Transferred Out (TO)	2(0.4)	0(0)
Total	**500(100)**	**50(100)**

Table 5: **Radiological Changes at the end of treatment in 100 (group one) and 50 (group two) ND PTB cases in Iwo.**

Radiological Change	Group One No of cases and (%)	Group Two No of cases and (%)
No Change	0(0)	0(0)
Slight/Minimal clearance	2(2)	1(2)
Moderate Clearance	10(10)	4(8)
Considerable (marked) clearance	88(88)	45(90)
Cavity Size Reduced or Disappeared: (Ten with cavities in group 1) (Two with cavities in group 2)	10(100)	2(100)
Total	**100(100)**	**50(100)**

DISCUSSION

Short-course combination chemotherapy, generally involving regimens that last for 6 to 8 months has become the standard treatment for newly diagnosed cases of tuberculosis[9,10,11]. The IUATLD[12] and WHO[8] also strongly recommend this. It has also been repeatedly demonstrated that any of the several six to eight month regimens can achieve extremely high success rates (<5 percent combined treatment failure and relapse)[13,14]. The SCC for ND PTB for 8 month as recommended above usually involve the use of rifampicin throughout the six months without the use of thiacetazone (Table 2). Primary drug resistance has been shown[15] to be reduced in the community with the use of these regimens.

The clinical outcome in the two groups in this study i.e. 8 - month and the 6 month regimens recorded high success rates as previously reported[13,14]. However, it should be emphasized that the use of Directly Observed Treatment Short-course (DOTS) also must have contributed to the clinical outcome noted. The five elements of DOTS[16] was used in this study. DOTS ensured a

comprehensive strategy which primary health services around the world are using to detect and cure TB patients. As an integral component of DOTS strategy, health workers counsel and observe their patient swallowing each dose of a powerful combination of anti-TB drugs and monitoring of the patients progress is undertaken until the patient is cured. Political, and financial commitment and a central, reliable and dependable drug supply are essential parts of the DOTS strategy. It should be emphasized that compliance which is a major impediment in TB treatment is controlled with DOTS. The use of TB Health Visitors was also used in this study as part of the DOTS strategy. Patients that failed to make their appointments with the health worker were contacted and their drugs administered at home in the presence of the TB Health Visitor.

Most hospitals in Nigeria today have no facility for the culture of *Mycobacterium tuberculosis*. Thus, it is therefore not possible to determine the sensitivity pattern. This could have been most helpful since the pandemic of multidrug-resistance tuberculosis has been well reported in most countries of the world'7. However, the standard combination of anti-TB drugs as used in this study have been recommended even when there is primary drug resistance in the community. Thus, the Nigerian NTCP recommended regimen for ND PTB is of added advantage in Nigeria where there are no studies done to document the pattern of drug resistance.

It was observed in this study that the reddish urine passed by the patients while on rifampicin had a negative effect on the patients even though they were specifically informed about this side-effect before they started chemotherapy. They could not pass urine in the public since the Yoruba culture views the passage of reddish urine as a sign of venereal disease (Atosi Aja in Yoruba). Thus, patients were happy when the rifampicin was stopped and thiacetazone started. This further supports the use of this regimen compared with the six month regimen that involves the use of rifampicin throughout. It is actually vesical schistosomiasis characterised by haematuria that is being confused with the reddish colouration of the urine in rifampicin use. Again, rifampicin is much more expensive compared with thiacetazone even though the six month regimen has the advantage of a shorter duration of the course.

Based on the result observed in this study, the author recommends that the recommended regimen for the ND cases of PTB by the NTCP of Nigeria in line with IUATLD and WHO using DOTS is good, cost-effective and should be used in Nigeria and should be adopted as a national policy for immediate implementation. DOTS however is not simple, easy or cheap. It requires total dedication, commitment, seriousness but at the end makes good economic sense and is cost effective.

ACKNOWLEDGEMENTS:

The author wishes to thank the Damien Foundation of Belgium based in Ibadan, Nigeria for the free drugs provision for all the study population. The Foundation also provided and maintained the motorcycle for the trained TB supervisor that visited the defaulted cases. The author is also appreciative of the effort and commitment of Mr J.A Akintunde, the TB supervisor Iwo Local Government Council who did all the home visitations.

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